LSD-25 & TRYPTAMINE SYNTHESES

OVERVIEW & REFERENCE GUIDE FOR PROFESSIONALS

by OTTO SNOW

PSYCHOACTIVE SYNTHESIS SERIES
VOLUME 2

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DEDICATION

I dedicate this book to future explorers and research scientists.

I am in appreciation of: A. Hofmann, A. Shulgin, J. Ott, D. Nichols, R. Manske, S. Cohen, S. Grof, R. Schultes, H. Osmond, T. Leary, S. Szára, R. Metzer, B. Aaronson, P. Stamets, R. Heim, and all those explorers (too numerous to name) who blazed a path into the great unknown, unraveling the mysteries of the brain-mind.

I want to thank the National Institute on Drug Abuse for their publications, and NIMH for their support of brain research.

"From the same jug of whiskey come tears for one
and laughter for another."
Sidney Cohen 1964

"Progress is a nice word, but change is its motivator
and change has its enemies."
Robert F. Kennedy

"Set and setting, expectation, and atmosphere
account for all specificity of reaction.
There is no "drug reaction" but always setting-plus-drug...
The drug (LSD-25) is just an instrument."
T. Leary and R. Alpert

"It should be our earnest intention
to insure that drugs not be employed
to debase mankind, but to serve it."
John F. Kennedy

"I see the true importance of LSD in the possibility of providing material aid to meditation aimed at the mystical experience of a deeper, comprehensive reality. Such a use accords entirely with the essence and working character of LSD as a sacred drug."
Albert Hofmann 1980

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☠ READER'S NOTICE ☠

☞ This reference guide is a tool for the legal profession and should not be misconstrued as a 'cookbook'. Publisher and author take no responsibility for inaccuracies, omissions, or typographical errors. All reactions are generalized. References are included for those seeking greater detail/descriptions on the construction of any specific molecule.

Chemicals and reactions are potentially toxic, explosive & lethal.

☞ This book is for information purposes only. No person is allowed to produce controlled substances without proper permits and authorization. To take/give substances for human consumption whether legal or illegal without a very thorough knowledge of the substance and the health (mental as well as physical) condition/s of the individual is destined to produce catastrophic results and legal ramifications.

LSD-25 & Tryptamine Syntheses is a reference guide on the preparation of:

substituted lysergamides,
substituted tryptamines,
neurotransmitters, neurotoxins,
immediate precursors, and precursors
from organic sources

Series and individual reactions are overviewed and extensively referenced. Many different routes are described on altering the molecular structures of known and unknown neurochemicals. The terms and explanations are simplified and interwoven with historical data. Excerpts from the Task Force Report: Narcotics and Drug Abuse, Annotations and Consultants' Papers (1967) are included to give the readers a look at the issues of major concern. Chemicals are indexed for quick reference to assist those investigating suspect laboratories to determine probable cause or reviewing cases to determine culpability, criminal activities or innocence of suspect/s.

This guide is an asset and a necessity for:
lawmakers, attorneys, teachers, counselors,
law enforcement and students alike.

INTRODUCTION

LSD-25 is the generic name of d-lysergic acid diethylamide. 9,10-Didehydro-N,N-6-methyl-ergoline-8ß-carboxamide is another one of the numerous ways to describe the molecule. Delysid is the trade name of the drug originally dispensed for research by Sandoz.

The molecule is the very cornerstone of neurochemistry. LSD has allowed neuroscientists to explore brain biochemistry; e.g. mental illness, serotonin receptors, serotonin receptor subtypes and numerous binding comparisons with other active molecules. Some drugs which have been found to block the effects of LSD are useful antipsychotics. Early studies described LSD as a psychotomimetic, yet this is a general term applied to all phantasmogens. LSD is listed as a hallucinogen in schedule one.

In clinical studies LSD (the drug) has been found to have a remarkable ability to treat disease from a psychological point of view. It has been extremely successful at aborting migraine headaches (Ling 1963) (Yensen 1989). It's most valued attribute is the prophylactic nature of the substance against migraines. This is the primary medical use (not FDA approved) of LSD-25 in the world. LSD-25 has been found not to cause chromosome damage (Irwin 1967) (Loughman 1967) as do many FDA approved psychotropic drugs.

LSD as well as MLD-41 and ALD-52 were were rejected for use as incapacitating weapons by both the CIA and KGB (see Weapons for Tomorrow) (Gertz 1996).

"Therapists working with small doses-such as 25-50 μg. of LSD-do so only to facilitate conventional therapy...

Types of conditions repeatedly stated to respond favorably to treatment with psychedelics include chronic alcoholism, criminal psychopathy, sexual deviations and neuroses, depressive states (exclusive of endogenous depression), phobias, anxiety neuroses, compulsive syndromes, and puberty neuroses. In addition, psychedelics have been used with autistic children, to make them more responsive and to improve behavior and attitudes; with terminal cancer patients, to ease both the physical pain and anguish of dying; and with adult schizophrenics, to condense the psychosis temporarily and to help predict its course of development...

Very small doses (on the order of 30 μg. of LSD) are sufficient to establish empathic bond...

It should be noted that when a therapist takes LSD, he enters a state in which he can communicate with schizophrenic patients in a direct, close, empathic fashion. This communication opens the door to effective psychological treatment for schizophrenia. The schizophrenic is lost in time, and a therapist who will enter the paths of his disordered thinking, once he can establish trust, can lead the patient out of the disorder. It is not always sufficient to call out from the forest's edge to rescue someone lost. One must sometimes go in himself."
Toward an Individual Psychedelic Psychotherapy, by Masters, R.E.L.; Houston, J.; in Psychedelics; The Uses and Implications of Hallucinogenic Drugs

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"Morgens Hertz, a Danish physician, described a patient whose long-standing stuttering condition disappeared following LSD treatment (Stafford & Golightly 1967). An American team of researchers found that schizophrenic children became more communicative following LSD treatment (Bender, Goldschmidt, and Siva Sankar 1956)." pg. 227
In Psychedelics; The Uses and Implications of Hallucinogenic Drugs;

Low doses of the drug (e.g. 25-50 μg.) are currently available in every city in the nation and most of the civilized world. The primary use (by youth) of the drug is a mood enhancer. This differs from the large dosages appearing in institutional, governmental and private sectors during the 1960's. Large dosages of the drug produce psychotic reactions. Large dosages of this drug are responsible for the unfortunate death of Mr. Olson (CIA) and has triggered latent psychoses in many individuals. Many lives were destroyed when sociopaths (eg. Dr. D. Ewen Cameron) used LSD as an instrument of torture against civilians (see The Search for the Manchurian Candidate and others).

Hoffer and Osmond spoke of an unknown substance called anti-S which is proposed as an endogenous anti-schizophrenic substance. Although this substance has not been discovered, the LSD-25 ligand has been found. It occurs to be elevated in psychotics. When psychotics are treated with psychotic drugs, LSD-25 ligand decreases. Although an intriguing molecule to study, this ligand also occurs in normals and has not been linked as the biochemical cause or marker of mental aberrations (Mehl 1977).

Psychotic reactions triggered by LSD have been reported to be aborted by neuroleptics, beta blockers and pargyline type molecules. These drugs block the neurochemical sequence of events that allow the drug to be active. More study on molecules which block or abort LSD effects should be researched further as it will lead to a better understanding of neurochemical mechanisms.

According to Drs. T. Leary and R. Alpert (referring to the entheogenic substances, mescaline, psilocybin, LSD):

"(1) these substances do alter consciousness. There is no dispute on this score.

(2) It is meaningless to talk more specifically about the "effect of the drug." Set and setting, expectation, and atmosphere account for all specificity of reaction. There is no "drug reaction" but always setting-plus-drug...

The drug is just an instrument."

Those who use LSD are primarily between the ages of 16 to 23. It is a white middle class to white middle-upper-class youth phenomena. Anyone interested in a comprehensive study of this should read:
LSD Still With Us After All These Years, by Henderson and Glass.

INVESTIGATING LSD SAMPLE TO OBTAIN INFORMATION AS TO SOURCE AND METHOD OF PRODUCTION

There are many LSD laboratories dotted across the nation which prepare small quantities of LSD for personal use and the use of close friends. These laboratories do not distribute to the public. There are several organized crime laboratories which turn out very large quantities of drugs, not limited to LSD.

Most major universities have a graduate student who prepares a small quantity (1 gram) as the 'right of passage' of the organic chemist. This LSD is generally given away or is sold at a cost under that of current market prices.

When there is no local source of LSD for college students the vacuum is immediately filled by LSD supplied by organized crime.

When drug intelligence is given a confiscated sample of LSD there are many tests which can be done to determine more about the source of the drug.

New make shift laboratories for public distribution do not have access to tablet machines (due to cost) and the drug itself tells a lot about the production techniques and knowledge of the chemist/s producing the drug.

The first forms of LSD from a laboratory usually appear on napkins, toilet paper or un-perforated blotter paper. The LSD may not have been titrated properly. By holding a sheet of blotter, impregnated with LSD, in front of a black light will show up imperfections in the the titration. LSD glows under a black light. When holding up a sheet of blotter it will glow evenly if the titration was done properly, if not, there will be spots that glow brighter than others and not at all in other areas of the paper. This is very dangerous. On one part of the blotter sheet the unit dosages maybe very high and other units, nothing at all. Improper titration techniques indicates irresponsible sheeting of the blotter.

When LSD is in the hands of drug intelligence much can be told about the drug, especially if it is improperly prepared. Each synthesis of LSD creates various isometric forms of the drug. Many forms exist: d-LSD-25 d-iso-LSD l-LSD-25 l-iso-LSD.

Only the d-LSD-25 is active, but improper purification techniques and synthesis leads to isometric mixtures in the end product.

Drug intelligence exists at a federal-international level. Local and state agencies are generally very inadequate at this. Many analytical laboratories are capable of doing very sophisticated microanalysis of drugs, yet the courts and state law enforcement agencies job out testing to determine if a controlled substance is present and usually want to know nothing more about the drug.

Making use of sophisticated analysis by appropriate laboratories at a local level would be a asset for law enforcement; it would allow them to be able to get more insight into the mode of the drug operation.

PROFILE OF LABORATORY CHEMIST

A degree of sophistication and knowledge of techniques to prepare LSD is necessary; LSD-25 is not 'easy to make.' A person who has no background in chemistry will not be able to understand chemical terms. Some who is not very familiar with sterile techniques will be unsuccessful at the cultivation of *Claviceps*. Chemists who work with indole molecules must be familiar with manipulating molecules which are sensitive to light, heat and air. This perquisite of "knowledge of technique" (being able to work with molecules under inert atmosphere, vacuum and protected from light) is not for amateurs. Organic chemists capable of mass producing LSD are usually working in cutting edge research and have little interest to psychedelicize the world. The primary objective of the 'new age' chemist is to explore the unexplored.

LSD is not made in bathtubs reminiscent of bathtub gin of yesterday's alcohol prohibitionist era. The construction of the LSD-25 molecule is rather complex and can be hazardous.

During the early sixties laboratories sprang up across the nation. Many of these laboratories supplied the intellectuals of the day. Today laboratories operate much the same way and the drug does not enter the public market place.

Organized crime entered the LSD arena post prohibition of LSD. The primary base for LSD production comes from ergotamine. Organized crime has obtained ergotamine by diversion of ergotamine from pharmacies.

Although the law makes no difference between the preparation of and manufacture of LSD, there is a major difference. An individual who makes a few grams of LSD is preparing LSD. An individual or group producing millions of doses of LSD is manufacturing. In the most simplistic of analogies, grandma may bake a few pies for the church bazaar, she is not manufacturing. When grandma goes national and distributes pies throughout the state and nation, she is manufacturing.

A few doses of LSD (for personal use) can not be created by the chemist because reaction products stick to the walls of the labware, filter papers, etc.. Micro synthesis is not something which is easily done. A minimum quantity in the preparation of LSD usually is in amounts from 1 to 3 grams.

LSD is generally sold by one hundred unit amounts. These squares are then broken up among friends. The one hundred quantity is standard for "window pane" and "blotter" types. At this amount the blotter can be examined under black light to determine even or uneven titration of the drug. The window pane or also called "clearlight" product has also appeared in one hundred quantities in small plastic vials. Several individual dosages can be sent off for analysis to determine dosage, if titration was done evenly and how the drug was synthesized.

"The blanket suppression of LSD and other psychedelics has been a complete disaster in that (1) it has seriously hindered proper research on these drugs; (2) it has created a profitable black market as it has raised the price; (3) it has embarrassed the police with an impossible assignment; (4) it has created the false fascination with fruit that is forbidden; (5) it has seriously impeded the normal work of courts of justice, and herded thousands of noncriminal types of people into already overcrowded prisons, which, as everyone knows, are schools of sodomy and for crime as a profession; (6) it has made users of psychedelics more susceptible to paranoia more than ever (For purposes of this summary I am including marijuana and hashish as psychedelics, though they do not have the potency of LSD)...

Western science is now delineating a new concept of man, not as a solitary ego within a wall of flesh, but as an organism which is what it is by virtue of its inseparability from the rest of the world... medicines which science has discovered... may prove to be the sacraments of this new religion."

The Joyous Cosmology, by Watts, A. 1970

There is no organized religion of LSD. The LSD experience is one of self awareness and discovery. In this context, LSD is used specificly for medical reasons/personal psychotherapy. Many individuals who occasionally take LSD may not smoke marijuana, cigarettes or use any other drugs for that matter.

Chemists who only prepare LSD-25 and no other drug are called "psychedelics men." These individuals are more akin to priests than criminals. The pyramid of associates that encompass the "high priest" number into the thousands. At the higher levels of the hierarchy, in close proximity to the priest, are also more psychedelics men and their families.

The procurement of chemicals is done through legal sources and provokes no attention from law enforcement. Drug distribution networks are shut down if drug problems arise in communities that abuse the sacrament.

Psychedelics men can not be called pushers, because they neither want people to abuse the drug, to adulterate (mix amphetamine or PCP with the product) or mishandle the drug. If we were to profile these individuals we could describe them as missionary or modern day apostles.

"Are the visions of a prophet revelation or disease? Does schizophrenia encompass both the delusional paranoiacs and the holy men whose trances have provided us with messages which many consider gospel? The psychedelic drugs have a contribution to make in the understanding of such matters. Under their influence episodes of psychotic disorganization are certainly possible. In other instances they have induced an experience of psychic integration which has been called identical with spontaneous religious experience by people who have known both states...

Self identity is completely lost, and the self and that which is outside the self fuse. The ordinary subjective-object relationships disappear, along with the conventional separateness of the external object. The extension of this egolessness can culminate in union or communion with the divine...

The Christian and yogin ethic agree that a thing has no intrinsic good or evil in it, but the manner of usage determines the evaluation to be placed on it. So, too, the psychedelics are neither "good" nor "bad" drugs; they have "good" and "bad" usages..."

The Beyond the Within, by Cohen, S. 1964

"publicity pressure threatens serious research not only with LSD but with the entire class of hallucinogenic drugs. We cannot put blame on the drugs; we can only put blame on the manner and the ways they are being used. It is my belief that it would be most unfortunate if we were to permit undue hysteria to destroy a valuable tool of science and evaporate an eventual hope for the many hopeless... Szára 1967

Many other investigators voiced similar concerns (Cohen 1966); Dahlberg 1966); Freedman 1966; Klee 1966) before congressional committees and other appropriate forums (Szára and Hollister 1973), but the situation remains the same today. Clinical research with these drugs essentially stopped, with the exception of Strassman's work on DMT (Strassman 1994) and some treatment-oriented work with LSD such as that on dying cancer patients (Yensen 1985)."

Szára 1994

"The technical review meeting entitled "Hallucinogens: An Update" was held July 13 and 14, 1992 in Bethesda, MD, the objectives of the meeting were: (1) to update current knowledge on hallucinogen research, especially relating to human studies; (2) to identify future preclinical and clinical research needs; (3) to discuss problems and possible solution associated with hallucinogen research especially relating to human studies; (4) to explore the potential therapeutic utility, if any, of classical hallucinogens; and (5) to address issues related to substance abuse such as how hallucinogen research can contribute, directly and indirectly, to abuse research and help prevent, ameliorate, and resolve problems associated with hallucinogen abuse."

Lin, G.C. 1994

"LSD does not act as a true medicament; rather it plays the role of a drug aid in the context of psychoanalytic and psychotherapeutic treatment and serves to channel the treatment more effectively and to shorten its duration."

Hofmann 1980

Approximately 9 % of the US population has taken or will take LSD. This has remained constant over the past 30 years. It is in the interests of both society and the scientific community that investigations of this drug are resumed.

Many psychoactive substances appear in Schedule 1 meaning:

1) The drug or other substance has a high potential for abuse.

2) The drug or other substance has no currently accepted medical use in treatment in the United States.

3) There is a lack of accepted safety for use of the drug or other substance under medical supervision.

Some substances which have little potential for abuse are still included in Schedule 1. N,N-Dimethyltryptamine (DMT), a neurotransmitter in the brain, is excreted in the urine of all individuals and is a controlled substance. Bufotenine has been reported not to be psychoactive (Lyttle 1993).

According to the Federal Code of Regulations the following molecules, their isomers (optical, geometric, positional) and their salts are currently listed under Schedule 1 as hallucinogenic substances:

N,N-Diethyltryptamine
N,N-Dimethyltryptamine
alpha-Ethyltryptamine
5-Hydroxy-N,N-dimethyltryptamine (Bufotenine)
4-Hydroxy-N,N-dimethyltryptamine (Psilocyn)
Lysergic acid diethylamide
o-Phosphoryl-4-hydroxy-N,N-dimethyltryptamine (Psilocybin)

Analogs, homologs and congeners of the previous molecules maybe subject to controls as described in the Analogue Act of 1986.

The following molecules are listed under Schedule 3:

Lysergic acid
Lysergic acid amide

The primary purpose of a scientist is to question, test, and continue researching; no action has any one specific purpose except that of seeking to transcend the unknown into the known. The most a scientist can do is hope to find something which will advance scientific knowledge which in turn will benefit the human race.

The very nature of neurochemistry involves the purchase of drug precursors as they are the precursors of many neurochemicals. Many chemicals that are used in the construction of neurochemicals are also used in clandestine laboratories, the only differences being the end products and their distribution.

To date, I have found no book that describes the synthesis of these molecules in a way in which lawyers, judges, law enforcement and students can easily comprehend. Reaction overviews, precursors, and various molecules are indexed and referenced for easy location of information.

"During clandestine laboratory investigation the forensic chemist may be asked to illustrate the synthetic route used by the defendant(s). For this reason, the forensic chemist should have a clear understanding of the synthetic routes available to the clandestine chemist."
(Cooper 1984)

In all laboratory raids, a forensic chemist must be present to evaluate the chemicals and paperwork. A chemist is also necessary to identify chemicals which may be hazardous and to shut down reactions.

Most laboratories have many chemicals. All individuals (law enforcement officers and suspects) are at risk of exposure to toxic chemicals if they are not contained; safety is paramount. Chemicals are safe as long as they are handled/stored and disposed of properly.

LSD laboratories will have specific equipment for the construction of molecules under an inert atmosphere (eg. gas tanks of nitrogen or argon) and distillation of solvents under reduced pressure (rotary/flash evaporator, vacuum pump, dry ice trap). Although this equipment can be used in the preparation of LSD; this equipment is also used by conscientious chemists so as not to contaminate the environment with solvents or those who are working with heat sensitive molecules.

It is the goal of law enforcement to stop illegal dangerous drugs and not to stop budding Einsteins from investigating the unknown. The more law enforcement know about the science of neurochemistry, the more equipped they will be at intercepting and dismantling illegal drug distribution laboratories.

CHAPTER ONE

RETROSPECT OF THE ILLEGALIZATION OF LSD-25

In 1967, The President's Commission On Law Enforcement and Administration of Justice compiled a public document titled: Task Force Report: Narcotics and Drug Abuse, Annotations and Consultants' Papers; referred to as TFR 1967. I will quote from the various consultants' reports to lay a foundation for a better understanding of prohibitionist policies and the long term effects of these policies.

"Narcotics and Drug Abuse

In 1962 a White House Conference on Narcotic and Drug Abuse was convened in recognition of the fact that drug traffic and abuse were growing and critical national concerns. Large quantities of drugs were moving in illicit traffic despite the best efforts of law enforcement agencies. Addiction to the familiar opiates, especially in big-city ghettos, was widespread. New stimulant, depressant, and hallucinogenic drugs, many of them under loose legal controls, were coming into wide misuse, often by students. The informed public was becoming increasingly aware of the social and economic damage of illicit drug taking.

Organized criminals engaged in drug traffic were making high profits. Drug addicts, to support their habits, were stealing millions of dollars worth of property every year and contributing to the public's fear of robbery and burglary. The police, the courts, the jails and prisons, and social-service agencies of all kinds were devoting great amounts of time, money and manpower to attempts to control drug abuse. Worst of all, thousands of human lives were being wasted.

This Commission has not and could not have undertaken to duplicate the comprehensive study and report on drug abuse so recently completed by another Presidential Commission. Yet

any study of law enforcement and the administration of criminal justice must of necessity include some reference to drug abuse and its associated problems. In the course of the discussion in this chapter, recommendations are made where they seem clearly advisable. In many instances these recommendations parallel ones made by the 1963 Commission.

Careful implementation, evaluation, and co-ordination of the new programs, some of which are not yet in operation will be absolutely essential. These are among today's first needs. New ideas are only a first step. Unless the programs they lead to are provided with sufficient money and manpower and are competently administered, no improvement in drug abuse problems can be expected.

Dangerous Drugs

Drugs in the in the hallucinogenic class have not yet been proven safe for medical purposes and are not legally available in drugstores. Their sole legitimate use at present is by qualified researchers in connection with investigation reported to and authorized by the Food and Drug Administration.[1]

The Hallucinogens

The only legal producer of LSD ceased manufacture in April 1966, and turned over its entire supply of the drug to the Federal Government. A few closely monitored experimental projects involving LSD are still in progress.[2]

The hallucinogenic drug traffic appears to be less profit oriented than others.[3]

In 1963 the President's Advisory Commission on Narcotic and Drug Abuse found that public and professional education in

the field was inadequate. It found the problem clouded by misconceptions and distorted by persistent fallacies.[4] Unfortunately these conclusions are as valid today as they were 3 years ago. Misinformation about drugs and their effects is still prevalent, and the measures taken by the Federal Government to correct them are still limited, fragmented, and sporadic. The National Clearinghouse for Mental Health Information within the National Institute of Mental Health (NIMH) collects and disseminates information, but drug abuse is only one of its many concerns, and its audience is largely made up of researchers and other specialists. Similarly, the educational efforts of the Bureau of Narcotics and the Bureau of Drug Abuse Control, while well intended and well executed, are not on the necessary scale. There is a clear present need for a single agency, having a specific mandate for education, to prepare and distribute a broad range of materials, from pamphlets to films, suitable for presentation to target segments of the public, such as college students. The materials must above all be factual.

References

1) Goddard, The Menace of Drug Abuse, Amer. Ed., May 1966.
2) Hearings of §. 2113, §. 2114,§. 2152, supra note 15, at 300 (testimony of Commioner Goddard).
3) Hearings on Organized Crime and Illicit Traffic in Narcotics Before the Permanent Subcommitte on Investigations of the Senate Government Operations Committe, 88th Congress, 1st & 2nd Sessions., pt. 3 (1964); Hearings on §. 2113, §. 2114, § 2152 Before a Special Subcommitte of the Senate Judiciary Committee, 89th Cong., 2nd Sess. (1966); Hearings on H.R. 2, supra note 39.
4) President's Advisory Commission on Narcotic and Drug Abuse, Final Rep. 21-30 (1963)."

"Mind-Altering Substances

Richard H. Blum
B.A., 1948 San Jose College
Ph.D., 1951 Stanford University

(excerpts from TFR 1967)

Summary of Current Knowledge

There is another fact to consider as part of the evaluation of drug use, drug abuse, and dangerous outcomes. Mind-altering drug use is common to mankind. Such drugs have been employed for millennia in almost all cultures. In our own work we have been able to identify only a few societies in the world today where no mind-altering drugs are used; these are small and isolated cultures.

Our own society puts great stress on mind-altering drugs as desirable products which are used in many acceptable ways (under medical supervision, as part of family home remedies, in self-medication, in social use (alcohol, tea parties, coffee klatches, etc.) and in private use (cigarettes, etc.)). In terms of drug use the rarest or most abnormal form of behavior is not to take any mind-altering drugs at all. Most adult Americans are users of drugs, many are frequent users of a wide variety of them. If one is to use the term "drug user" it applies to nearly all of us. Given this fact, the frequently expressed concern about drug "use" might better be put in terms of drug "abuse." "Abuse" of course is also ill defined. Presumably judgments of abuse rest on such questions as (a) How much of the drug, or drug combinations, is taken and how is intake distributed? (b) Does the person take disapproved drugs? (for example, heroin instead of alcohol, marijuana instead of tranquilizers), (c) Does he take drugs in unapproved settings? (an adolescent drinking wine with a gang rather than at the family dinner table, an adult taking amphetamines without medical approval), (d) Does his behavior under drugs offer some real risk to himself or to

others? (Our primary concern here: Crime, accidents, suicide, but also dependency, medical danger, etc.) There are no doubt, other factors that would be revealed should one do a study of how people come to judge that drug "abuse" is occurring.

The critical point for us is the realization that "use," "abuse," and "risk" are emotionally charged terms that may be based on hidden determinants or open assumption that cannot be shown to have a factual basis.

To offer one conclusion at the outset, it is that current evaluations of drug use by the public, by the mass media, and by some officials, are often emotional. The programs, laws, and recommendations that arise from these emotional responses may well be inappropriate if the steps taken do not match drug use realities.

Hallucinogen Use in the United States

No reliable epidemiological or "drug" census data exist. Use appears to be concentrated in young adults age 20 to 35 but there are signs of rather rapid diffusion to high school age levels and less rapidly to middle and older age adults. Employed in medical research, LSD has been given to small numbers of psychiatric patients, alcoholics, schizophrenic children and has been tested on terminal (dying) patients as a means of easing their distress. Employed by religious and philosophical seekers it has been given in institutions and centers, and other settings. These institutional uses account for only a fraction of current use; impressionistic but probably trustworthy reports indicate expanding social and private use of the drug derived from black market sources. Ease of transport and synthesis make LSD distribution easy. The use of other hallucinogens, peyote for example (1), has been fairly well confined to traditional (Indian) groups ...

As has been the history with many mind-altering drugs, the pattern of LSD diffusion has been overtime from older prestigeful persons downward to younger less prestigeful ones, also from institutionalized medical and religious (or pseudoreligious) settings to more secular use.[2] With secular use, a drug becomes "social," use is subject to less constraint, and greater variety of personalities, settings, and expectations are involved. At the present time, it would be unwise to venture any estimate of the number of Americans who have tried one or another hallucinogen; any numerical estimates must be suspect. One may presume that given a condition of continued easy availability of the drug plus wide publicity about its favorable effects, use would expand rapidly; historically the epidemic spread of tobacco smoking, opium use, and distilled alcoholic beverages provide illustrations. What effect current legislation to control manufacture, distribution, sale and in some States, possession, will have on LSD use cannot be said at this time. It has generally been the case that interest in drugs can be channeled but not repressed.

Characteristics of Users

LSD, DMT, etc., were first confined to physicians and other research workers and then spread to their subjects, patients, families, and friends. Until a few years ago, LSD remained limited to an "elite" group of successful professionals, artists, and communications industry personnel, their families and friends. These same groups still appear to be using hallucinogens, but the concentration of use appears to have shifted to younger persons. Among teenagers, motorcycle club members, delinquents, urban poor and minorities, etc., there are reports (Senate Subcommittee on Government Reorganization, 1966) of spreading interest, suggesting the expected diffusion down the socioeconomic scale. No common psychological or

sociological features may be expected among the users of any secular and social drug; different people take drugs for different reasons.

Verified Risks

Crime associated with hallucinogen use appears to have been minimal. Police reports before a California legislative committee emphasized disturbances of the peace (1965) than felonies. It would appear that insofar as decent citizens take hallucinogens their behavior will remain lawful. We expect that with the expansion of hallucinogen use to delinquent groups-and perhaps because it is unlawful in some States, so that its use becomes criminal-a greater frequency of crime will be reported.

Comment

We agree with the present plans of the National Institutes of Health-notably spurred on by Senators Robert Kennedy and Abraham Ribicoff-to conduct epidemiological research on expanding American drug use and to finance further research on the hallucinogens. We also agree with the present policy of the Food and Drug Administration setting up controls over the manufacture and distribution of LSD but not making possession a law violation.

Recommendations

We are aware that there is disagreement about whether or not a particular drug use (especially alcohol and LSD) is a special case rather then part of a generalized drug picture. On the basis of our assumption and because of the differing positions others hold, it is recommended that general studies be continued which attend to all aspects of drug use, seeking to define both similarities and differences by drug or classes of drug as well as by user or population use habit characteristics.

As a final recommendation we would request of the mass media an emphasis on less sensational reporting and feature writing in regard to LSD and other drugs, would invite the public to give their legislators a moratorium during which time knowledge can be evaluated and reasonable approaches proposed, and would generally suggest as a matter of school and public health education that an effort be made to admit to uncertainty and to restrain emotion in the consideration of drug effects and the changing pattern of drug use.

Education

The delinquent nonaddicts also had more negative information about opiates during their critical exposure period (age 16)-they had seen overdoses or had watched a "cold turkey" withdrawal. The importance of information is compatible with other studies on other drugs. For example, LSD users[3] were informed about benefits; controls not taking it had more information about dangers or nonpleasurable effects. A cautionary and tangential point: One who might desire to immunize a child against heroin use by educational efforts must not equate information-giving with information acceptance. He must also be aware that information given in a frightening or noncredible manner is likely to be rejected.

Other Drug Use

In the early period of their work Chein et al. reports[4] found that the majority (87 percent) of New York slum heroin users had first tried marijuana; however in their study of street gangs they found a different pattern where marijuana smoking had not preceded heroin use; they do not give a figure to document that statement. They do observe that marijuana was more commonly used than heroin and that 15 percent of their

controls had smoked marijuana. The section on marijuana in this report describes how other populations (city dwellers in California, professionals using LSD, and professional controls not using LSD, etc.) had 10 to 15 percent marijuana experience, and that such experience was not associated for most persons with any later experimentation with heroin.

Weighing Risks

With regard to the psychoactive (mind-altering) drugs, what constitutes high gain and what constitutes high risk and who shall decide what these are and how shall that decision affect marketing of the drug? Some tranquilizers which are quite useful in treatment of mental illness produce jaundice-like symptoms and central nervous system (extrapyramidal) symptoms which affect body musculature; yet in the mentally ill (are) these side effects... acceptable (?)

Who is to decide what risks a man may take for himself? Are drug risks decisions to have a different base than those in parachute skydiving, cave exploring, or travel in dangerous lands? When a man says it affects himself only but others point out that it is his family which may suffer or the community which must pay for his care, who has the right to decide on weighing the risks?

LSD

Should it be prohibited from any but experimental medical use with criminal sanctions for possession for any other purpose or, at the other extreme, should it be freely available to anyone to use as he sees fit. Varying positions are held by law enforcement personnel (for control and punitive laws on possession), medical personnel (mostly for medical but no other use), some academicians, theologians, intellectuals, and artist (for nonmedical use but in some controlled setting), members of the government movement (for unrestricted use). We admit to over generalization; no vocational group has but one position. Our intent is only to establish points on the continuum to indicate major sources of support.

Public Concern

Public beliefs are no doubt shaped by many forces, some these facts of the kind that scientists generate or confirm, some of the forces being strong emotion which, while very real, may lead to distorted views of the facts of drug effects. In addition, public opinion is no doubt shaped by misinformation received at the hands of the press, various interest groups (narcotics police, temperance people, etc.), from back-fence folklore and the like. It is our impression, not supported by evidence, that public opinion on drug matters does carry a heavy overload of emotion; by overload we mean emotions stronger than those deserved by the facts of extent of drug use and kinds of effects alone. As we indicated in an earlier section, we suspect that the emotion not only reflect persona and cultural conflicts over drugs use per se, but reflect very genuine concern about how others do act. People say they are worried about drugs; what they are really worried about is people. The facts are that people do behave badly toward one another, raping, robbing, killing, being unpredictable, and doing all of these terrible things contrary to the morals and rules of our society and ourselves. Furthermore, offenders do these things irrationally, that is contrary to their own long-term best interests. It is difficult to understand why, for behavioral scientists as for anyone else. Our society is undergoing very rapid changes which each day bring us new problems; each citizen is faced with new challenges to his thinking, his adjustment, and which create for him further uncertainty about the future. Some of these changes are in the nature of decreasing the old and familiar ways of dealing with people; more and more strangers are about, the cities are bigger, people are on the move, the younger generation talks of revolution and Negroes speak of "black power." It can all be very unsettling. The facts of life are unsettling too. Crime, at least on the basis of police reports, is on the increase; and increase in violence and property loss considerably more than one would expect from population increases alone. People are afraid. A recent public opinion poll (California, Field poll, June 1966) showed crime and delinquency mentioned as a public problem by more people (a majority in fact) than any other single thing.

When looking for explanations for mystifying human conduct, the "explanation" people arrive at often only point to a scapegoat or shift the mystery to something else. People ask, "I wonder what got into

him?" or "What possessed him?" as if it were an outside force that had taken over, since it is painful to imagine an inner force so beastly as to lead to killing eight nurses or shooting dozens of people from a library tower. In ancient Greek drama the answer would have been that a god guided the arm or clouded the eyes of the person, the god being the one who willed the act. In the Middle Ages devils or demons (some of them demoted Greek gods in historical fact) took over, "it was the Devil that entered him" becoming the answer. But, with modern technology, the Devil is manufactured and has become a drug, instead. "Drug Crazed Killer Shoots Two" as a newspaper caption example. Or consider the first psychiatrist interviewed after the awful Chicago murders of eight nurses. Without benefit of an interview with the accused (Speck), the good doctor was quoted in the news as saying, "He must have been on drugs." (He was not.)

Factual Risks

No matter how we look at it each point of view should serve to remind us it is (1) a person who uses a drug and person who commits a crime. We should also be reminded that the much more common case occurs where (2) a person uses a drug and does not commit a crime, or (3) where a person does not use a drug and does commit a crime or (4) does not use a (specified) drug and does not commit a crime. In any event there is a link between drug use, other offenses, and the person himself and it is likely that these links will be very complex and their exact nature will remain uncertain for some time to come. At this point, lest we forget, we should add the fifth most frequent case, epidemiologically speaking, to the foregoing; to with, (5) nearly all of us are mind-altering drug users and nearly all of us have committed offenses, but very few of us have been identified either as drug-dependent persons or as offenders.

A Professional Sample

In the course of a study of LSD users we gathered a group of 47 controls, nonusers who were like the users in age and professional status, etc.[5] It happened that our user sample was a very respectable and successful, for the most part, professional group; they are our controls. They included professors, mental health professionals, ministers, and the like. We cannot contend that they are representative

of professional people, but if we are fortunate, their beliefs will not be greatly at odds with others like them. We discussed drug matters with them at some length (or gave them a detailed questionnaire). We found that most of these "square" controls considered the police as unduly punitive in enforcing drug laws, for example against marijuana use. The majority condemned present punitive narcotics legislation; most wanted more humane handling and greater emphasis on treatment. Only one-sixth wanted stricter controls. Those who were angry about drug issues, rather than being upset with drug users or other narcotic users, were, instead, hostile to the police. Some controls tended, we think quite unfairly, to degrade the knowledge and the humane feelings of the police as a group. In any event, these professionals considered the present criminal laws and the police enforcing them as out of line with desirable social policy.

A Narcotics Officer Sample

In another study [6] a small sample of narcotics officers (31 of many more asked to cooperate) were asked about their views on drug offenders and about ideal dispositions for them. Ranking groups on a scale of menace to the community, heroin addicts were ranked as less of a menace than the Communist Party but more of a menace than syndicated crime, burglary rings, and confidence men. Marijuana users were ranked as less of a menace than any of the foregoing but more of a menace than the Mafia, white supremacists, crooked real estate operators, and the like. LSD users raking lower, were more of a menace than the John Birch Society. Asked to recommend ideal punishments for typical offenders, drug peddlers received an average sentence of 6-10 years in prison, the same as given to rapists and armed robbers. Marijuana users along with prostitutes, auto boosters, and income tax evaders were sentenced together for from 1 day to 1 year in jail. LSD users came off more easily, being grouped with common drunks, beatniks, homosexuals, adulterers, and speeding drivers for probation with no time served... when asked what the public views were toward users of illegal but presumably nonaddicting drugs (marijuana, LSD), officers most often said the general public was fearful of the spread of drugs in the community, was uninformed, was confused, disgusted at drug practices, and revolted by even nonaddictive illicit drug use effects.

It is our impression, not based on formal interview or questionnaire data, but on acquaintance with men who serve as narcotics officers, that they are also aware of the special "publics" who are not in support of a punitive approach to nonmedical drug use, as for example the professional people in our LSD study control group. Some of these officers would be interested in furthering an exchange with professionals to share points of view and to arrive at points of agreement[7].

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3) Blum and Associates, "Utopiates, A study of the Use and Users of LSD-25." New York: Atherton Press, 1964

4) Chein, Gerard, Lee and Rosen, "The Road to H." New York: Basic Books Inc., 1964.

5) Blum, Richard H. and Associates, Utopiates. N.Y. Atherton Press, 1964

6) Blum and Whal, "Police Views on Drug Use," in Blum and Associates, Utopiates. N.Y.: Atherton Press, 1964

7) Lindsmith, 1965"

"Proposals for Dangerous Drug Legislation

by Michael P. Rosenthal
A.B., 1956, Columbia College
L.L.B., 1959, Columbia Law School

(excerpts from TFR 1967)

Experimental and occasional weekend use of LSD appears to be common.[1]

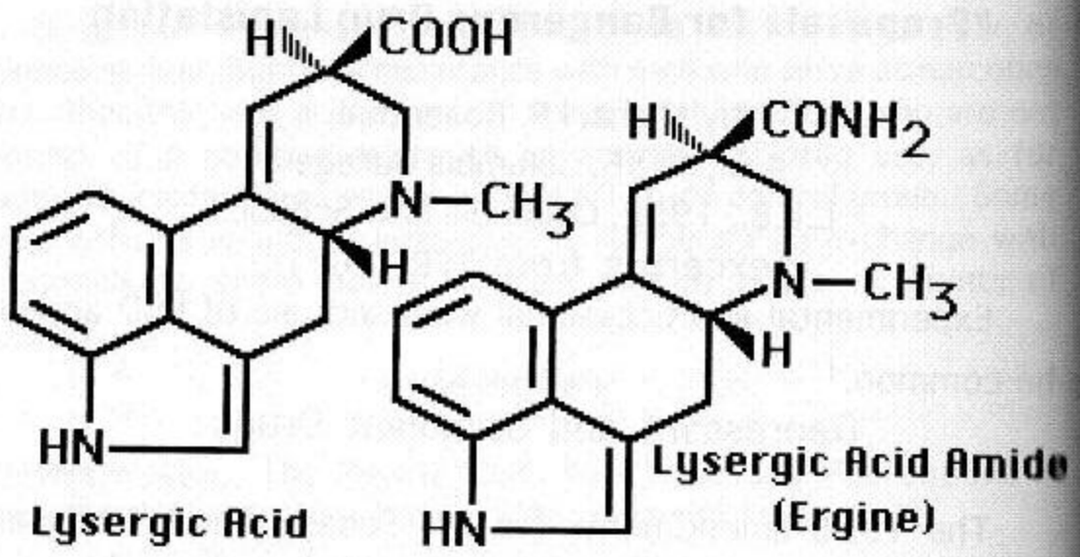
Depressant and Stimulant Drugs

The 1965 amendments (to the Federal Food, Drug, and Cosmetic Act) apply to "depressant or stimulant drugs."

The most important aspect of the coverage of the term "depressant or stimulant drugs," however, is found in that part of the definition which includes:

"any drug which contains any quantity of a substance which the Secretary (of Health, Education, and Welfare), after investigation has found to have, and by regulation designates as having, a potential for abuse because of its depressant or stimulant effect on the central nervous system or its hallucinogenic effect..."

Only recently the Secretary has designated a number of well known tranquilizers and nonbarbiturate sedatives as well as a number of hallucinogens including peyote and mescaline (active ingredient of peyote) and LSD.[2] The manufacturers of three of the tranquilizers have challenged the designation, and hearings are currently in progress.[3] Two substances used in the manufacture of LSD-lysergic acid and lysergic acid amide have also been designated as "depressant or stimulant drugs" under this part of the definition because they have been found by the FDA to be depressants, and because when either is processed to manufacture LSD a "powerful" hallucinogen is created.[4]



Recommendations Dealing With State Law

It is recommended either that the provision of the Federa act which exempts from the prohibition on unauthorize possession, possession "(1) for personal use (of the possesso or a member of this household, (2) for administration to a animal owned by him or a member of his household" and whic puts the burden of proving that the possession was not for an of the purposes mentioned on unauthorized possession with purpose to sell or otherwise dispose of a "depressant o stimulant drug," but exempting possession (1) for the person use of a member of the possessor's household, or (2) fo administration to an animal owned by the possessor or member of his household, should be included in any Stat legislation. State law should not prohibit simple possession o use.

A model State act should also contain a provision to the effect that nothing in it should be deemed to interfere with any right protected by that provision of the State constitution which in substance guarantees the free exercise of religion or with any right protected by the free exercise clause of the first amendment to the United States Constitution.

It is also recommended that unauthorized manufacture of a controlled substance drug should not be the subject of a criminal prohibition under a model act unless it is committed with a purpose to sell or otherwise dispose of such a drug. When it is not committed with such a purpose it may appropriately be a civil violation.

Use and Possession Offenses

The recommendations herein are not based on the view that criminal treatment of use or simple possession is unconstitutional. It is recognized that policy and constitutional considerations may tend to merge. However, the recommendations are based on considerations of what is believed to be proper policy. While it is possible to argue that some of the reasoning Robinson v. California[5] indicates that punishment for use or even simple possession is unconstitutional, the Supreme Court there specifically stated that possession may still be treated as a crime.[6] As to use, it was less clear.[7] Most States and lower Federal courts have narrowly read Robinson and have held that use may still be made criminal.[8]

Possession for Household or Animal Use

It is recommended that the exception to the Federal possession offense for possession for use of household members and for administration to household animals should be retained for controlled drugs which are used in the ordinary practice of medicine. While it is undesirable for a person to give a tranquilizer or barbiturate prescribed for him to another member of his household, the practice is so common that it is not believed the criminal laws should reach it.

LSD

In some respects, whether simple possession or use of L should be an offense is a more difficult question to answer than similar question posed with respect to the commonly used "medica depressant and stimulant drugs. The possible effects of use may deemed by some more undesirable than the effects of addiction barbiturates or nonbarbiturate sedatives or habituation amphetamines. Upon this question the author does not pass judgme Unlike the "medically" depressant and stimulant drugs, which have date been controlled, LSD does not have widespread legitimate use medical practice. Its medical use is totally experimental.[9] It can introduced or delivered in interstate commerce only und investigational new drug approvals issued to qualified investigators the FDA.[10] Neither would use of LSD be considered normal by most the community. And though it may be fairly common for a person to gi a tranquilizer to a friend or relative, it would not, except in certa groups, be common or considered normal to so distribute LSD.

Even though it is believed that neither simple possession nor u should be prohibited at this time, it must be recognized that if t problem cannot be controlled through trafficking offenses and if adver affects are found on a large scale, additional legislation may be in ord in the future. Such legislation could take the form of a civil violati with a sanction other than interference with personal liberty.

Unauthorized Manufacture

It is recommended that unauthorized manufacture should not be criminal offense unless it is done with purpose to sell or otherwi dispose of a controlled drug. Illicit manufacturers usually manufactur "depressant or stimulant drugs" to distribute them. However, som controlled drugs may be made on a small scale for personal use. Thus, i is possible that some individuals may be making LSD solely for the own use. Many of the same reasons which support the exemption o persons who without authorization possess controlled drugs solely fo their own use from criminal liability also support their exemption from criminal liability for unauthorized manufacture. Even more than possession, unauthorized manufacture is an offense preparatory to

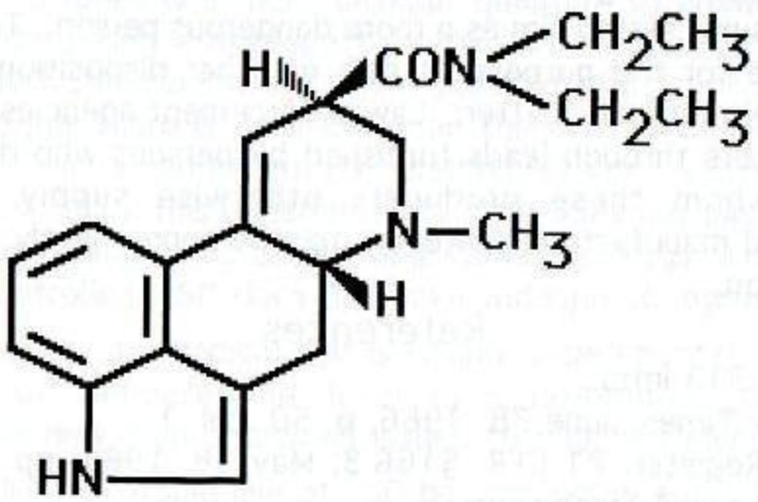
distribution. If the manufacture is not for distribution and if the user is not to be punished for his use, the manufacturer who manufactures for his own use should not be punished either. The mere fact that the user makes the drug himself instead of obtaining it in some other fashion does not stamp him as a more dangerous person. To prove that manufacture for the purpose of sale or other disposition should not ordinarily be a difficult matter. Law enforcement agencies often trace illicit producers through leads furnished by persons who distribute for them or whom these producers otherwise supply. "Simple" unauthorized manufacture, however, may be appropriately treated as a civil violation.

References

1) See note 313 infra.
2) New York Times, June 28, 1966, p. 50, col. 1.
3) Federal Register, 21 CFR, §166.3, May 18, 1966, pp. 7245, cols. 3 and 7246, col. 1 (proposed).
4) Bulletin on Narcotics, No. 1, 15,21 (1963).
5) In Robinson, 370 U.S. 660 (1962), the Supreme Court held that the cruel and unusual punishment clause of the 8th amendment, made obligatory upon the States by the 14th amendment, barred a State from treating narcotics addiction as a crime. Its reasoning would bar making addiction to dangerous drugs a crime.
6) "A State might impose criminal sanctions, for example, unauthorized manufacture, prescription, sale, purchase, or possession of narcotics within its borders." 370 U.S. at 664.
7) See the dissenting opinion of Mr. Justice White, 370 U.S. at 685, 688.
8) See note, "Alcoholism, public intoxication and the law," 2 Colum. J. of Law and Soc. Prob. 109, n. 142 at 128 (1966).
9) N.Y. Med. Society Report, 22 N.Y. Medicine, No. 9, 3, 5, (May 5, 1966).
10) Statement of Comm'r Goddard before the Subcommittee on Executive Reorganization of the Senate Committee on Government Operations, May 24, 1966 see note 191 supra."

CHAPTER TWO: LYSERGAMIDES

N, N-Dialkyl Substituted d-Lysergamides



LSD-25
(d-Lysergic Acid Diethylamide)

LSD-25 was first synthesized in 1938. It was not until 1943 that its powerful psychoactive effects were discovered by Dr. Albert Hofmann.

"...five years after the first synthesis, to produce LSD once again so that a sample could be given to pharmacological department for further tests. This was quite unusual; experimental substances, as a rule were definetly stricken from the research program if once found to be lacking in pharmacological interest." (Hofmann 1980; in LSD)

According to Dr. Hofmann, "Possibly a bit of the LSD solution had contacted my fingertips during the crystallization, and a trace of the substance was absorbed through the skin." (Hofmann 1980; in LSD)

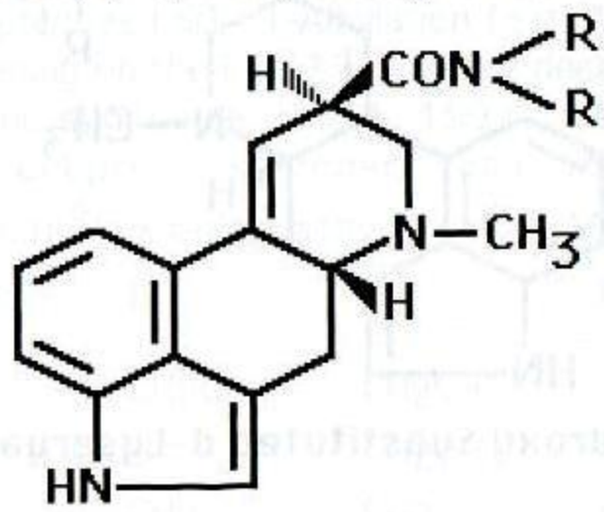
"LSD is in fact not absorbed through skin; Hofmann most likely touched his LSD-contaminated fingers to his mouth."
(Henderson 1994)

...the rest is history.

"LSD finds an application in medicine, by helping patients in psychoanalysis and psychotherapy to perceive their problems in their true significance." (Hofmann 1980; in LSD)

LSD-25 is mildly active at 25 μg. At this dosage the effects slightly resemble tricyclic antidepressants. At 50 μg. the effects are mild mood elevation and bonding; increased sense of awareness. At 75 μg. to 100 μg. the effects are mild depersonalization, mollusk like color visualizations with eyes both open and closed. At approximately 100 μg. entheogenic effects occur; oneness with all that is; unity with God. Colorful swirling mandalas and wavering of wood grain are also vivid. At higher dosages there are rather powerful hallucinogenic effects such as walls melting and breathing, spiders from wrinkles in sheets, distortion of time and space with intense visual color syntheses.

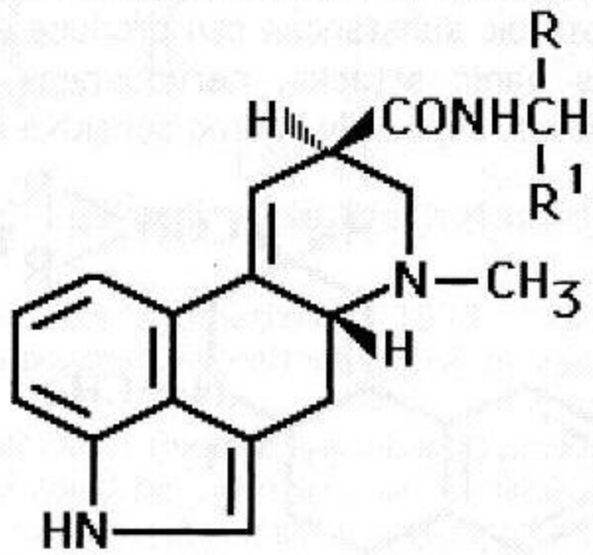
All psychotropic substances can produce serious adverse effects such as panic attacks, nervousness, paranoia and temporary psychoses, especially in drug sensitive individuals.



Abbreviated Name		R	R1
LSD-25		CH_2CH_3	CH_2CH_3
DAM-57		CH_3	CH_3
LAE-32		H	CH_2CH_3
LA-111	Ergine	H	H
LSM		$-CH_2CH_2OCH_2CH_2-$	

See LSD - A Total Study pg. 151 for analog activity comparisons.

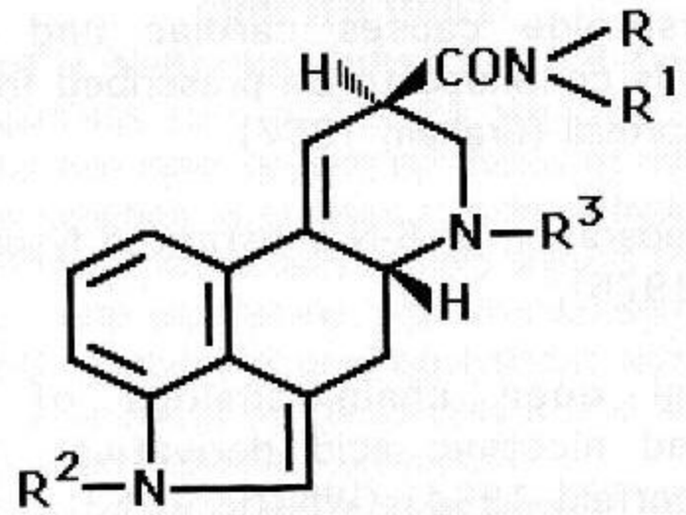
LAE-32 (d-Lysergic acid ethylamide) and DAM-5 (d-Lysergic acid dimethylamide) have been reported to be activ between 500 to 1,400 µgs. (Ott 1993) (Jacob 1994). LA-11 also called ergine (d-lysergic acid amide) is the active constituen of an Aztec entheogen called Ololuiqui (*Rivea corymbosa*). It is feeble psychoactive which is active in humans at 1 mg. LS (d-lysergic acid morpholide) is active between 300 to 600 µg (Grogerty 1957). The *Convolvulaceae* (morning glories) gener of plants contain varying amounts of ergine and the non-activ erginine (d-iso-lysergic acid amide). Some strains of *Clavicep paspali* also contain varying amounts of both ergine and erginin



N-1-Hydroxy Substituted d-Lysergamides

Chemical Name	R	R^1
Ergonovine (Ergometrine)	CH_3	CH_2OH
d-Lysergic acid N-(1-hydroxyethylamide)	CH_3	OH

Ergonovine and d-lysergic acid N-(1-hydroxyethylamide) occur in some *Convolvulaceae* and also some strains of *Clavicep paspali*. Both produce oxytocic action (contractions of the uterus), mydriasis (dilated pupils) and hyperthermia.



1-Alkyl & N-6 Substituted d-Lysergamides

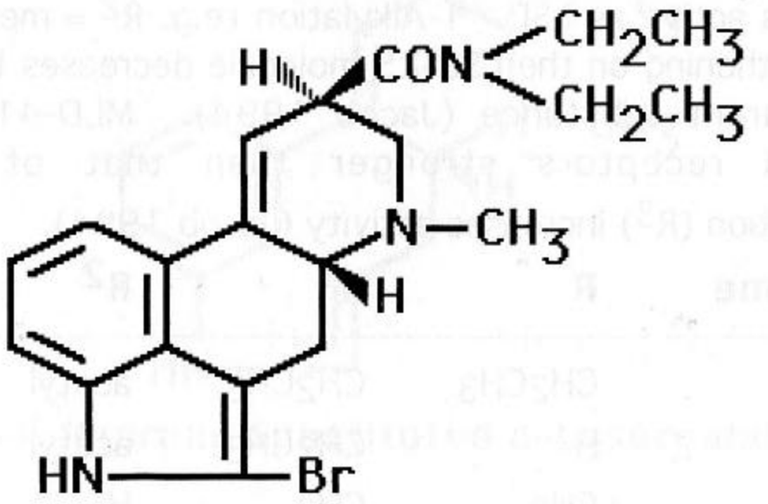
ALD-52 (1-acetyl-d-lysergic acid diethylamide) is equally as active a LSD-25. ALA-10 (1-acetyl-d-lysergic acid ethylamine) is 1/10 as active as LSD. 1-Alkylation (e.g. R^2 = methyl, ethyl) chain lengthening on the LSD-25 molecule decreases the activity of the parent substance (Jacob 1994). MLD-41 binds to serotonin receptors stronger than that of LSD-25. N-6 Alkylation (R^3) increases activity (Jacob 1994).

Code Name	R	R^1	R^2	R^3
ALD-52	CH_2CH_3	CH_2CH_3	acetyl	CH_3
ALA-10	H	CH_2CH_3	acetyl	CH_3
DAM-57	CH_3	CH_3	H	CH_3
LAE-32	H	CH_2CH_3	H	CH_3
MLD-41	CH_2CH_3	CH_2CH_3	CH_3	CH_3
MLA-74	H	CH_2CH_3	CH_3	CH_3
ALLYLAD	CH_2CH_3	CH_2CH_3	H	ally
BULAD	CH_2CH_3	CH_2CH_3	H	butyl
ETHLAD	CH_2CH_3	CH_2CH_3	H	ethyl
PROLAD	CH_2CH_3	CH_2CH_3	H	propyl

Methysergide causes cardiac and pulmonary fibrosis, yet is continued to be prescribed for migraines with FDA approval (Graham 1967)

For preparation of 6-N substituted lysergamides: (Niwaguchi 1976).

Several open chain analogs of LSD and 6-substituted nicotinic acid derivatives have been created: (Lehrfeld 1964) (Whittle 1963). For chloro, nitro and amino analogs of LSD and psilocin see (McKay 1963).



2-Bromlysergic Acid Diethylamide

2-Bromlysergic acid diethylamide (BOL-148) is inactive. 2-Oxy lysergic acid diethylamide is the metabolite of LSD-25; it is also inactive.

CHAPTER THREE:
Synthesis of N, N-Dialkyl Substituted d-Lysergamides

Lysergamides such as LSD-25 are created by various methods. The two most popular syntheses of these molecules are the Curtis Reaction which uses anhydrous hydrazine and the Garbrecht Synthesis which uses gamma sulfuric anhydride. The Curtis Reaction uses ergotamine, ergonovine, lysergic acid or any molecule which contains d or d-iso lysergic acid as a parent molecule. The Garbrecht Synthesis uses d or d-iso lysergic acid monohydrate as an immediate precursor.

The Curtis Reaction

Preparation of d-iso Lysergic Acid Hydrazide

One part (weight) of ergot alkaloid (salt) (eg. ergine hydrochloride, ergotamine hydrochloride) is heated (90 degrees C.) with four parts (weight) of anhydrous hydrazine for one hour. Or

One part (weight; eg. one gram) of ergot alkaloid (base) (eg. ergine, ergometrine, ergotamine) is heated (120 degrees C.) with five parts anhydrous hydrazine (eg. 5 mL) in one part (eg. 1 mL) of glacial acetic acid (or inorganic acid with pK value less than five) for a half hour.

The mixture is then diluted with water (approx. 20 mL per gram of alkaloid). The water and hydrazine hydrate are distilled off under vacuum or reduced pressure. The residue is mixed with ether and tartaric acid. The aqueous layer is separated, made alkaline and extracted with chloroform. The chloroform solution is evaporated to leave the d-iso-lysergic acid hydrazide.

Starting Mol.: Ergot alkaloid (Salt or Base) Ref. : Hofmann 1966
Reagent: anhydrous Hydrazine
Product: d-iso-Lysergic acid hydrazide Yield: 80 - 95 %

Starting Molecule: Ergotamine Reference: (Stoll 1943)
Reagent: anhydrous Hydrazine Yield: 70 %
Product: d,l-iso-Lysergic acid hydrazide (racemic)

d-iso-Lysergic Acid Azide From d-iso-Lysergic Acid Hydrazide

At 0 degrees C., a 40 mL of 0.1 normal solution of hydrochloric acid is added to a mixture of 1 gram of lysergic acid hydrazine in 35 mL of 0.1 normal solution of hydrochloric acid and 35 mL of 0.1 normal solution of sodium nitrite. Lysergic acid azide hydrochloride precipitates. Five minutes later, 13 mL of a normal solution of sodium carbonate is added. Lysergic acid azide is extracted with 350 mL of benzene. The benzene is evaporated to leave residue of d-iso-lysergic acid azide.

Starting Molecule: d-iso-Lysergic acid hydrazide
Product: d-iso-Lysergic acid azide
Reference: (Hofmann 1966) (Sandoz 1950) (Stoll 1943)

---

d-iso-LSD From d-iso-Lysergic Acid Azide

The d-iso-lysergic acid azide is dissolved in 100 mL of ether. 1 mL of diethylamine is added to the solution and placed in the dark for 24 hours. The solution is evaporated to leave a residue of d-iso-lysergic acid diethylamide.

Starting Molecule: d-iso-Lysergic acid azide
Reagent: Diethylamine
Product: d-iso-Lysergic acid diethylamide
Reference: (Sandoz 1946) (Stoll 1943)

Starting Molecule: d-iso-Lysergic acid azide
Reagent: d-2-Aminobutanol-1
Product: d-iso-Lysergic acid-d-1-hydroxybutylamide-2
Reference: (Stoll 1941)

The Garbrecht Synthesis

The Garbrecht Synthesis uses salts of lysergic acid monohydrate such as potassium, lithium, calcium, barium, ammonium etc. See citations for preparation of these salts. The salt is suspended with gamma sulfuric anhydride in a solvent which is inert to the reaction. Hexane, acetonitrile, dimethylsulfoxide (DMSO), dimethylformamide, dioxane and many other solvents have been used successfully with this reaction. Solvents must be anhydrous. Reactions are carried out at no higher temperature then 35 degrees as tarry substances are formed with elevated temperatures. At 0 degrees is best, but then the melting point of the solvent used must be taken into consideration.

Solution A) 1 Gram of potassium d-lysergic acid monohydrate is mixed with 14 mL of anhydrous hexane.
Solution B) 0.5 Gram gamma sulfuric anhydride and 14 mL of acetonitrile are mixed. The solutions are kept at 5 degrees C.

Solution B is added with stirring to solution A and stirring continued for five minutes.

A solution of 1.1 grams of diethylamine is dissolved in 14 mL of ether with stirring and poured into the solution. Allow to set for five minutes. The solution is then extracted three times with 100 mL of water. The aqueous extracts are combined and saturated with salt. The solution is then extracted three times with 100 mL of ethylene dichloride or appropriate solvent. The solvent is then evaporated to leave a residue of d-iso-lysergic acid diethylamide and d-lysergic acid diethylamide.

Starting Molecule: Potassium d-lysergic acid monohydrate
Reagent: Diethylamine
Product: d-Lysergic acid diethylamide & d-iso-LSD
Reference: (Garbrecht 1956, 1959)

Starting Molecule: Potassium d-lysergic acid monohydrate
Reagent: 2-Aminopropan-1-ol
Product: Ergonovine & Ergonovinine Ref.: (Garbrecht 1956; 1959)

Starting Molecule: Potassium d-lysergic acid monohydrate
Reagent: l-Ephedrine
Prdcts: d & d-iso-Lysergic acid ephedride Ref.: (Garbrecht 1956)

Starting Molecule: Potassium d-lysergic acid monohydrate
Reagent: Morpholine
Product: d & d-iso-Lysergic acid morpholide
Reference: (Garbrecht 1956)

Epimerization of d-iso-LSD into d-LSD

d-iso-Lysergic acid diethylamide is dissolved in a 0.4 molar methanolic solution of potassium hydroxide and allowed to stand in the dark for approximately 1 to 2 hours. Carbon dioxide gas is bubbled through the solution forming a paste of potassium carbonate. The paste of potassium carbonate/alcohol/LSD is mixed with 50 parts ether and filtered; this is repeated. The filtered solutions are dried and evaporated to leave a mixture of d-lysergic acid diethylamide and d-iso-lysergic acid diethylamide which can be separated by fractional crystallization or chromatography.

Starting Molecule: d-iso-Lysergic acid-d-1-hydroxybutylamide-2
Reagent: Potassium hydroxide Ref.: (Stoll 1941)
Products: (0.4 parts) d-Lysergic acid-d-1-hydroxybutylamide-2
(0.5-0.6 parts) d-iso-Lysergic acid-d-1-hydroxybutylamide-2

Starting Molecule: Ergonovinine Reagent: Potassium hydroxide
Products: Ergonovinine & ergonovine Ref.: (Pioch 1956)

For epimerization of d-iso-lysergic acid to d-lysergic acid see (Semonsky 1965). For epimerization of d-iso-LSD to d-LSD (Cerny 1968).

Fractional Crystallization of LSD-25

A residue of d-iso-lysergic acid diethylamide and d-lysergic acid diethylamide is dissolved in a minimum quantity of methanol (wood alcohol). A 20 % solution of maleic acid (or d-tartaric acid) in methanol is added. The LSD-25 maleate or tartarate spontaneously crystallizes and is suction filtered from the solution. The fluffy needle crystals are then washed with cold methanol.

Mother liquors are made slightly alkaline with aqueous ammonium hydroxide and extracted with ethylene dichloride. The ethylene dichloride solution is evaporated to leave a residue of d-iso-lysergic acid diethylamide. d-iso-LSD can then be epimerized and the d-lysergic acid diethylamide separated from the mixture.

Starting Molecules: d-iso-N-Cyclohexyllysergamide
d-N-Cyclohexyllysergamide
Reagents: Maleic acid
Product: d-N-Cyclohexyllysergamide maleate
Reference: (Garbrecht 1958; Johnson 1973; Stoll 1939)

Separation of d-Lysergamides from d-iso-Lysergamides by Chromatography

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Starting Molecules: Ergine & iso-Ergine (Erginine)
Product: Ergine
Reference: (Sandoz 1962)

Starting Molecules : d-Lysergic acid diethylamide & d-iso-LSD
Product: d-Lysergic acid diethylamide
Reference: (Pioch 1956; Sandoz 1946)

Alternative Syntheses of Lysergamides

Alternative sythneses produce mixed esters, amides, etc. and are generally non specific in acylatation. Yet illegal drug laboratories use what they have available. In many cases the end products are mixures of inactive lysergamides and active lysergamides. These impurites are chemical 'finger prints' for the forensic chemist which not only tells what chemicals were used in the synthesis, but can also be useful in determaining the knowledge of the chemist.

Starting Molecule: Lysergic acid monohydrate
Reagents: Cyclohexylamine L-2-Amino-1-propanol
Phosphorous oxychloride
Product: d-N-Cyclohexyllysergamide Ref.: (Johnson 1973)

Starting Molecule: Lysergic acid monohydrate
Reagents: Methanesulfonic acid anhydride
L-2-Amino-1-propanol Dimethylformamide
Product: Ergonovine Ref.: (Garbrecht 1959)

Starting Molecule: anhydrous Lysergic acid
Reagents: Phosgene Diethylamine
Dimethylformamide
Product: N,N-Diethyl-d-lysergamide Reference: (Patelli 1964)

Starting Molecule: Lysergic acid
Reagents: Trifluoroacetic acid anhydride Diethylamine
Acetonitrile or various solvents
Product: d-iso-Lysergic acid diethylamide Ref.: (Pioch 1956)

Starting Molecule: d-iso-Lysergic acid hydrazide
Reagents : Acetylacetone d-2-Aminobutanol-1
Product: d-iso-Lysergic acid-d-1-hydroxybutylamide-2
Reference: (Hofmann 1963)

CHAPTER FOUR: LYSERGIC ACID

The annual production of lysergic acid exceeds 12 thousand kilos. In 1976 the kilogram price was between $3000 to $4000 according to Heinz G. Floss. Lysergic acid is the precursor for molecules which:

1) increase cerebral blood circulation
2) antimigraine medications
3) affect activity of hypothalmic-pituitary system including the regulation of prolactin from the pituitary.
4) the construction of molecules of unknown activity for use in research and potential medications.

Lysergic acid can be created:

1) semisyntheticly or totally synthetic, but it is not cost effective.
2) by isolation from field cultivated ergot (from ergot alkaloids).
3) by fermentation of *Claviceps* species (from ergot alkaloids).
4) by extraction from *Convolvulaceae* seeds (from ergoline alkaloids).

Arcamone of Farmitalia S.A. (*Claviceps paspali)*, and Kobel at Sandoz Laboratories (*Claviceps purpurea)* developed the fermentation of *Claviceps* fungus for industrial production. Reference: (Floss 1976)(Ott 1993)

Ergot contains approximately 1% alkaloids. *Convolvulaceae* seeds contain varying amounts of alkaloids. Submerged fermentation of *Claviceps* is the most economical source for ergot alkaloids.

CHAPTER: FIVE
ERGOLINE ALKALOIDS FROM CONVOLVULACEAE

Convolvulaceae is a widely distributed family of plants. I would suggest readers pick up a copy of The Botany and Chemistry of Hallucinogens and also Pharmacotheon for a more detailed look at *Convolvulaceae* history and constituents. The seeds of various species (*Argyreia*, *Ipomoea*, *Stictocardia*, and *Cuscuta*) have been analyzed to contain ergolines:

Chemical Name	Alternative Names
d-Lysergic acid amide	Ergine
d-iso-Lysergic acid amide	iso-Ergine
Lysergic acid-alpha-hydroxyethylamine	
iso-Lysergic acid-alpha-hydroxyethylamine	
Ergonovine	Ergometrine
Ergonovinine	Ergometrinine
Chanoclavine-I	
Chanoclavine-II	
Penniclavine	
Elymoclavine	
Agroclavine	

RIVEA CORYMBOSA

The Aztecs used the seeds of several species for divination purposes in religious ceremonies. "Ololiuqui" is the seeds from *Rivea corymbosa* (also called *Turbina corymbosa*). The plant itself is called "coaxihuitl," "the snake-plant."

Rivea corymbosa produces beautiful white flowers and grows in Mexico, West Indies, Texas, Southern California and Southern Florida. The alkaloid content of the seeds range from a low of 0.021 % to a high of 0.060 % according to Marderosian (1966) and Youngken. Ref.: (Taber 1962)

MORNING GLORIES

The seeds of Ipomoea violacea were used by the Aztecs in religious ceremonies. They were called "tlitliltzin". These seeds are used religiously/medicinally by the Zapotecs, Mazatecs, Mixtecs, Chinantecs in Oaxaca and are called "Badoh negro." Other species (*Ipomoea rubro-caerulea praecox*, *Ipomoea purpurea* have tested positive for indole alkaloids.) *Ipomoea violacea* is commercially available in many horticultural species:

Heavenly Blue
Pearly Gates
Flying Saucers
Wedding Bells
Summer Skies
Blue Star

Alkaloids vary from a low of 0.005 % to a high of 0.079 %.
References: (Genest 1966) (Marderosian 1964; 1966) (Nikolin 1972) (Niwaguchi 1969) (Taber 1963)

ARGYREIA NERVOSA

Hawaiian Baby Woodrose (*Argyreia nervosa*) also called woolly wood roses are beautiful vines that grow in Hawaii, Mexico, and the southern parts of Texas, California and Florida. The plant is believed to originate from India. The Hindus used the roots in the treatment of inflammatory disease. The alkaloid constituents of seeds range from a low of 0.5 % to a high of 0.9%. Ergine and isoergine make up approximately 54 % of the total alkaloids.

The leaves of the morning glory contain only traces of ergolines. References: (Chao 1973) (Hylin 1965). Ingestion of seeds described produces lethargy, nauseousness and vomiting.

Extraction of Ergoline Alkaloids From Seeds

Method A

Pulverized seeds (100 grams) must be defatted before extraction of alkaloids. Naphtha or petroleum ether are suitable solvents for fat extraction of the seeds. The seeds can be refluxed in the solvent or they can be refluxed in a Soxhlet extractor. The seed mash is then filtered from the solvent. Total extraction of fats is accomplished when new solvent extract leaves no greasy residue on evaporation.

The seed mush is then allowed to dry of solvent, mixed with 500 mL of 10 % ammonium hydroxide (strong ammonia water) and extracted with ether or appropriate solvent. Evaporation of the solvent leaves the alkaloids. Reference: (Genest 1965)

Method B

100 Grams of pulverized seeds is mixed with 50 grams of sodium bicarbonate and 100 mL of water. 100 Grams of anhydrous sodium sulfate are mixed to leave the mass dry and granular. The mass is extracted three times with one liter of ethyl acetate. The ethyl acetate solutions are combined and evaporated to leave the alkaloid residue. Reference: (Marderosian 1966)

Ergoline alkaloids will decompose in light, heat and air. Tartrate and maleate salts are less susceptible to destruction.

CHAPTER SIX:
LIFE HISTORY AND POISONUS PROPERTIES OF CLAVICEPS PASPALI

Journal of Agricultural Research (1916) 7: (2) 401-407

By H.B. Brown

"During the last decade Paspalum dilatatum Poir. has attained considerable prominence as a forge grass in various parts of the South. One serious objection to its use, however, is that forge poisoning frequently results among cattle feeding on it. Brown and Ranck showed that the poisonous property is due to Claviceps paspali Stevens and Hall, a fungus that infects the grass very generally. This species was described by Stevens and Hall in 1910. Norton observed this fungus on P. dilatatum in Maryland in 1902. He suspected that it was poisonous, but carried on no feeding experiments to determine this.

Since September, 1914, the writer has been making a study of the life history of Claviceps paspali and its growth and distribution in the region about the Mississippi Agricultural College. In this region the fungus infects Paspalum dilatatum very generally, a few weeks after the grass heads out at least 90 per cent of the old heads showing infection.

Life History of The Fungus

Sclerotia produced during the summer and autumn drop to the ground when the old grass head sheds it spikelets, and lie on the ground until spring. They may be found at any time during the winter and spring by searching in the litter on the ground where infected Paspalum dilatatum grew the season before. Sclerotia gathered during the winter and placed in moist chambers kept at room temperature will germinate in 20 to 30 days, but it is the writer's experience that sclerotia forced in this way do not produce as many nor as large and vigorous stromata as those that germinate in the normal way. After a few days on rainy weather about the middle of May, sclerotia germinating on the ground may be expected. They were first found on May 10 in 1915 and on May 21 in 1906. In each case this was just after the host plant had begun to flower.

Sclerotia of Claviceps paspali when mature are globular in shape, 2 to 4 mm. in diameter, irregularly roughened on the surface, and yellowish gray in color; the interior is homogeneous in structure and contains a considerable quantity of oil. Germinating sclerotia produce from one to several stromata, usually two or three, with slender whitish stalks 3 to 15 mm. in length, and heads about 1 mm. in diameter. The heads are roughened over the surface owing to projecting perithecial necks and are at first whitish in color, later becoming rather bright yellow, and finally brownish.

A vertical section of a stromatic head shows numerous flask-shaped perithecia embedded in the outer part of the head. Thus forming small pimple-like projections. Each perithecium contains numerous slender, cylindrical asci, 150 to 170μ in length; at the outer end of each ascus there is a thimble-like knob fitting over the end. The wall of the ascus is so thin that it can not be distinguished clearly. The ascospores are filiform and hyalin, being a little less than 1μ in diameter and 70 to 100μ in length. There are probably eight spores in an ascus, although not more than seven were counted with certainty. It was not possible to count the spores when inside an ascus, as they are hyalin and packed together closely, and it was a rather difficult matter to count them as the ascus disintegrated.

Mature stromatic heads from sclerotia just gathered from the field when allowed to dry slightly and then moistened exuded asci very freely. The asci go to pieces quickly after escaping from the perithecia and liberate the spores. A change of moisture conditions in the field will cause spores to be deposited on the surface of the stromatic head, where they are in position to be picked up by insects and chance to rub against the head. The stromata are somewhat tough and leathery and last for several days. If the ground becomes dry during their regular period they dry out, but revive with the coming of moisture and again shed spores. No stromata were found in the field after July 2.

Flowers of Paspalum dilatatum inoculated with ascospores by rubbing stromatic heads against stigmas and spikelets of the grass heads showed abundant evidence of infection in seven days. Flowers on control plants showed no infection. (Both inoculated plants and controls were kept under bell jars.) In the field, infected heads are not found for

several days after the sclerotia germinate. They are first noticed on June 8 in 1915 and on June 12 in 1916, being, respectively, 29 and 22 days after germinating sclerotia were first found. In 1915, infected or diseased heads were not plentiful in the fields until about July 12. Preceding this date there were several days of rainy weather. In 1916, similar observations were made. Diseased heads became very common during July, following several weeks of rain. On August 1, 1916, they were more plentiful than since the autumn of 1914.

In the fields the first infection of the season is doubtless carried by insects. Running over the ground, they are likely to rub against the stromatic heads, which are covered with ascospores, and, climbing up the grass clumps to take flight, may carry ascospores to the grass flowers and produce infection. That infection does not take place often is evidenced by the fact that the disease is slow in getting a start after the sclerotia germinate.

The infecting fungus attacks the pistil of the grass flower, and in a few days the ovary is almost entirely destroyed, a mass of fungus tissue filling the space it occupied. There is a mass of fungus tissue between the glumes of a grass spikelet a week after infection. The central part of the grass flower has been replaced by homogeneous tissue, while around the edge are numerous tufts of hyphae standing at right angels to the central mass. Each tuft contains a number of hyphae. The digital ends of these hyphae, or certain of them, enlarge and for conidia or sphacelia spores. The spores are hyalin but show granules when stained, oblong, about 5μ wide x 15μ long. They are produced in great abundance and are carried from the hyphae on which they were produced by a droplet of honeydew, a sticky, sweetish exudation of the fungus tissue. Insects of many kinds feed on this honeydew and carry infection by means of spores clinging to their bodies. Hand inoculations, which were made by smearing honeydew containing sphacelia spores on flower stigmas, produced infections that were exuding honeydew and sphacelia spores freely within the space of a week. This result was obtained in the case of plants kept under bell jars, and also with plants inoculated in the field. Sphacelia spores frequently germinate in the droplet of honeydew and give it a whitish appearance.

The sphacelia stage in which honeydew is exuded lasts but a few days. If the weather is dry, the whole grass head is likely to become dry and dead, and no further development occurs. Or, again, honeydew may become infected with a species of Fusarium or Cladosporium and growth be stopped. If weather conditions are favorable, the solid mass of fungus tissue, constituting the bulk of the sphacelia tissue, continues to enlarge and soon forces the glumes of the spikelets apart. These masses are young sclerotia. In some cases within a week after the sphacelia stage was at its height the young sclerotia were projecting from between the glumes of the spikelet and were 1-2 mm. in diameter. Following this, some of the sclerotia continue to enlarge, attaining a maximum dia. of about 4 mm. and characters as outlined above. During Sept. and Oct. the largest sclerotia are to be found; and are also most plentiful then."

A FEW HOST PLANTS TO CLAVICEPS PASPALI

Latin Name	Common Name	Perennial
P. distichum	Knotgrass	
P. dilatatum	Dallis-Grass	Perennial
P. floridanum	Florida Paspalum	
P. intermedium		
P. langei	Rustyseed Paspalum	Perennial
P. laeve		Perennial
P. longipilum		
P. pubescens		
P. pubiflorum	Hairy-Seed Paspalum	Perennial
P. urvillei	Vasey-Grass	Perennial

References: (Gieger 1939) (Gröger 1961) (LeFebvre 1939).
See also The Story of Ergot

HOST PLANTS RESISTANT TO ARTIFICIAL INOCULATION OF CLAVICEPS PASPALI

Latin Name	Common Name	Perennial
P. lividum	Long-Tom	Perennial
P. malacophyllum	Ribbed	Perennial
P. notatum	Bahia Grass	Perennial
P. supinum		

ERGOT SIZE IN REFERENCE TO SIZE OF SPIKELET

Paspalum Species	Spikelet Length	Size of Ergot Length x Diameter
dilatatum	3-4 mm.	3-4.5 mm. in diameter
laeve	2.4-3.4 mm.	3-4.5 mm. in diameter
urvillei	2.2-2.7 mm.	1-2 mm. x 1-1.5 mm.

CHAPTER SEVEN:
A METHOD OF DEVELOPING CLAVICEPS PURPUREA:

Phytopathology (1911) 1:(2) 50-53
By H.H. Whetzel and Donald Reddick

"Since the publication of the beautiful illustrations of *Claviceps purpurea* by Tulasne in 1853, this fungus has been a favorite type used by authors of text books as representative of fleshy pyrenomycetes. Sclerotia of this fungus are found commonly enough but the students rarely see the perithecial stage. This is probably not because stromata are not formed commonly, but because they are not sought at the right time, and because of their small size. In an attempt to develop stromata for class demonstration and use, we have met with such abundant success that our methods of procedure may be of interest both as to method and scientifically as well. Some earlier attempts by one of us to develop the ascigerous stage from dried sclerotia had proven failures and taking our cue from nature we thought to simulate natural conditions to as great an extent as possible.

About August 10, 1907, one of us collected quantities of the sclerotia of *Claviceps purpurea* Tul. in the heads of rye (*Secale* cereals) which had come up "volunteer" in a field of oats near Swan, Noble Co., IN.

On the later date quantities of sclerotia of the several collections were enclosed separately in ordinary screen wire and put on the ground under a grape arbor. They were not disturbed until April 6, 1908. On that date, they were brought to the laboratory, placed on moist sand in a covered slender dish and kept at room temperature.

On April 18, 1908, we noticed evidence of germination in the sclerotia from the rye. There were tardy developments in all cases so that it was May 23rd, before all stromata had developed.

April 19, 1908 (some of the stromata at least 24 hours old). The first indication of development is the rupture of the cortex of the sclerotium and appearance of a white globose head 0.5 mm. in diameter. This ascigerous portion is pushed up on a stem, increases in diameter and is sharply differentiated from the stem. The stem is pale lilac; broad at the base and tapering toward the apex.

April 22, 1908, "no indications of perithecia at this date; the head has enlarged slightly and has become pale straw color; the stem has lengthened perceptibly."

April, 24, 1908, "yesterday the old stromata began to show punctures indicating the ostiola of the perithecia; today these are quite distinct, but the asci are still decidedly immature. The ascigerous portion is flesh color to pale fawn; up to 1.5 mm. in diameter. The stems are lilac at the apex and fade out nearly white at the base; up to 1 cm. long. One sclerotium has 12 stromata developing from it." A white radiating tuft of hyphae developed about the base of many of the stems, especially after the stromata were nearly mature.

On April 19, 1908, sclerotia from the same collection, kept dry in the laboratory over winter, were placed on moist sand in a slender dish. May 23, 1908, there were no indications of development in any case.

At that time we had not seen an excellent paper by Rostowzew which is written in Russian and in which he makes the point, by experiment, "the sclerotia of ergot (*Claviceps purpurea* Tul.) preserve their vitality for one year only. This viability is lost in less than one year, if they are subjected to complete drying out while in the resting stage."

In attempting to make photographs we have noticed the very decided tendency of the stem to twist and turn. In order to obtain a good photograph without blurring, it was necessary to keep the stromata on a wet background and covered with a thin glass dish while the process of focusing was performed. The cover was removed and the water taken away with a blotter only long enough to make the exposure.

The twisting was also noticed in the culture dishes, but it was not given any study. Rostowzew studied this carefully and made some extremely interesting observations. He finds that this movement is an adaptation for the discharge of spores in a vertical direction. That the discharge of spores is only in a vertical direction was demonstrated by the placing of cover glasses in various positions near a mature stroma. Spores were obtained only on the glass suspended directly over the stroma, never at the sides nor beneath.

No inoculation experiments were made by us as no grasses were in flower as early as May 24th at Ithaca. Quantities of the sphacelial stage on rye were found in June, 1908, by one of us, in the locality from which sclerotia were obtained in 1907. Cornell Univ., Ithaca, NY"

A simple germination is described in Molds, Mushrooms and Mycotoxins by Christensen, pub. by Minn. Press which follows:

"For the class demonstration of germinating sclerotia, I have collected the sclerotia of ergot from Minnesota rye in the fall and have put these on the surface of moist sand, then have put them in an incubator at 4 to 5 degrees C (40-42 degrees F) and have left them until spring, at which time they were exposed to outdoor weather; after a few weeks, they began to germinate. If the sclerotia are kept moist and at 3 to 4 degrees C (about 40 degrees F) for a couple of months, then held at 14 degrees C (57 degrees F), they will germinate by mid-December. By manipulation of the temperature-time schedule, that is, the sclerotia can be induced to germinate at various times, but in nature they germinate when it is their time to germinate - when their host plants are flowering."

References: (Henson 1940) (Lewis 1962)

CHAPTER EIGHT:

CLAVICEPS PURPUREA CULTIVATION AND STRAIN SELECTION

Ergots are obtained from the field and stored in the refrigerator in a tightly sealed container so as not to infect anything in the refrigerator. Ergot is poisonous.

Several dozen Petri dishes are sterilized by heat. 350 degrees F for three and one half hours. The dishes are then allowed to cool.

Preparation of Media

Claviceps will grow on various organic substrates. Potato Dextrose Agar (PDA) and Malt Extract Agar (MEA) are the most popular.

Malt Extract Agar (MEA)

Malt Extract: ------- 10 grams
Peptone: ---------- 2.5 grams
Agar: ------------- 7.5 grams
Distilled Water: ----- 500 mL

Potato Dextrose Agar

150 Grams of diced potatoes are boiled in 250 mL of water until cooked. The cooked potatoes are strained through cheese cloth and water is added to bring the solution to 500 mL 7.5 Grams of agar are dissolved in the water with heating. 10 Grams of glucose (corn syrup) are added.

The media is sterilized in an autoclave (pressure cooker) for 30 minutes and allowed to cool in the pressure cooker. When the sides of the pressure cooker are just a little warm to touch the media is ready to pour into the sterilized Petri dishes.

If the media is not allowed to cool it will form water condensation in the dishes and increases the rate of contamination. If the media is allowed to cool too much it will gel and then will not pour.

The media should be poured as rapidly as possible so as not to contaminate the dishes with air born microbes. The dishes are allowed to gel and then stored in a refrigerator until ready for inoculation with ergot.

INOCULATION OF CULTURES

Sterile conditions are a must. Several scalpels or Exacto knifes are placed in a drinking glass and the glass is then filled with alcohol (wood, denatured, rubbing) to sterilize the knives. An ergot is grasped at its ends by thumb and index fingers of both hands. The ergot is then snapped in half. Inside the ergot is a white, gray or pinkish material, this is the mycelium.

Take one of the scalpels from the alcohol solution and allow the alcohol to drip free from the blade. A small piece of the mycelium is then taken from one half of the ergot and placed onto the media. This technique must be done rapidly as opening of the culture dishes for extended periods will produce contamination. Several dozen dishes must be cultured as contamination will occur and during strain selection many of the cultures will be discarded.

STRAIN SELECTION

The sclerotial form of *Claviceps purpurea*, ergot, is a heterokaryotic fungus, that is a multi strain fungus containing multinucleated cells. Sclerotial forms of the fungus produce alkaloids. Condial forms of the fungus are uninucleated. They do not produce alkaloids unless the condia are germinated and the hyphia are mated.

Petri dishes inoculated with an inner piece from the ergot will form many cultures, many will be contaminated, others will be non-heterokaryotic, many will form spores (condia) and not form alkaloids. Strain selection is necessary to isolate a strain which will be a high alkaloid producer.

Sectors will form in some of the cultures. These sectors may be yellowish white, white, cream, violet, brown etc. Some of the cultures will form large colonies with no sectors, or late forming sectors, these are generally the heterokaryotic cultures. Heterokaryotic cultures are most like the original sclerotial form of the fungus. It is the form which will generally produce the highest percentage of alkaloids in submerged cultures.

References: (Abou-Chaar 1961) (Amici 1966; 1967) (Hareven 1970) (Mizrahi 1968)

After several strains have been obtained, they are then cultivated in larger quantities. Industrially this is done in large fermenters which are just large pressure cookers. Large equipment is impractical for most individuals. Canning jars or pressure cookers can be successfully used. Sterilization of media is done as described elsewhere in this book.

Industrial Fermentation Equipment: (Cleverdon 1955) (Dworschack 1954) (Fuld 1957)

CHAPTER: NINE
PRODUCTION OF ALKALOIDS BY CLAVICEPS CULTURES

Ergot alkaloids can be produced from the submerged culture of *Claviceps*. *Claviceps purpurea* and *Claviceps paspali* both can produce alkaloids. The production of ergot alkaloids in submerged culture resembles that of antibiotic production.

Mannitol, sucrose (cane sugar) and glucose (corn sugar) are the best sugars used by the fungus for a carbon source. Mannitol maybe sterilized by autoclave. Sucrose and glucose should be Seitz filtered or they will produce lower levels of alkaloids. Sorbitol cuts alkaloid production in half and maltose drops alkaloid production to 1/7 th that of mannitol.

Inorganic salts are also added to the culture media as a nutrition source.

The following culture media for *Claviceps purpurea* was developed by Amici, Minghetti, Tonolo and Spalla (1964) at Societa Farmaceutici Italia. It is listed in grams per liter:

50 grams mannitol
10 grams succinic acid
1 gram potassium phosphate
0.3 gram magnesium heptahydrate
1 gram chick pea meal
0.01 gram ferric sulfate heptahydrate
0.01 gram zinc sulfate heptahydrate
0.001 gram manganese sulfate heptahydrate

The pH is adjusted to 5.2 with aqueous ammonia. Yields are approximately 1 gram of alkaloids per liter.

The following culture media uses mannitol as a carbon source. Mannitol maybe replaced by sucrose or glucose but should be sterilized by running through a Seitz filter.

Media by A. Tonolo (1966): 20 % mannitol
3 % peptone
tap water

Adjust pH to 6.2 Incubation at 24 degrees C. for 8 to 10 days produces 800 to 1,400 μg ergotamine per mL from *Claviceps purpurea*.

The following media has been used by Amici, Minghetti, Scotti, Spalla, and Tognoli (1967). Media T25 (in grams per liter):

300 grams sucrose
15 grams citric acid
0.5 gram potassium phosphate
0.5 gram magnesium sulfate heptahydrate
0.1 gram yeast extract
0.12 gram potassium chloride
0.007 gram ferric sulfate heptahydrate
0.006 gram zinc sulfate heptahydrate
tap water, pH 5.2 with aqueous ammonia

Claviceps purpurea alkaloid production reaches 1,800 μg (per mL) of ergotamine after an 18 day fermentation.

The following culture media was developed by Mary, Kelleher and Schwarting (1965) at the University of Connecticut, Storrs. The research was conducted on the cultivation of *Claviceps paspali*. It was a study of the inorganic requirements of this species of *Claviceps*. Mycelial fragments were homogenized before inoculation. This produced uniformity among cultures and reduced the duration of fermentation:

Medium B: 5 % mannitol
3 % succinic acid
0.1 % potassium phosphate, monobasic

Inorganic Salts added to basil media (per liter):

800 mg.	Magnesium sulfate heptahydrate
304 mg.	Calcium nitrate tetrahydrate
5.3 mg.	Zinc sulfate heptahydrate
53.3 mg.	Ferric sulfate heptahydrate
200.0 mg.	Sodium Sulfate
120.0 mg.	Sodium nitrate
219.0 mg.	Potassium chloride
9.0 mg.	Magnesium sulfate tetrahydrate
0.75 mg.	Potassium iodide
0.054 mg.	Aluminum chloride hexahydrate
2.50 mg.	Boric acid
7.45 mg.	Cupric sulfate pentahydrate

The media is adjusted to a pH of 5.2 with aqueous ammonia and autoclaved. Alkaloid production peaked at 728 μg per mL in nine days.

When calcium, iron, zinc or magnesium are omitted from the culture media, there is a decrease in both growth and alkaloid production. The omission of copper caused a decrease in alkaloid production. In media which only contained zinc, iron, magnesium and calcium did not reach peak alkaloid production in controls containing complete salt/nutrient supplements. Alkaloid production was increased in these cultures when supplemented with manganese and copper salts.

More Fermentations

References: (Abou-Chaar 1961) (Adams 1964) (Amici 1967; 1969) (Arcamone 1961) (Brady 1960) (Kelleher 1969; 1971) (Ogunlana 1969) (Pacifici 1962; 1963) (Societa Farmaceutici Italia 1961) (Taber 1966)

These are just a few of the many cultures that appear in the literature and have been used in the production of ergot alkaloids in submerged cultures.

CHAPTER TEN:
LYSERGIC ACID EXTRACTION FROM CULTURES

Various solvent mixtures can be used to extract ergot alkaloids from dried (calcium chloride or magnesium chloride can be used when less than 5 grams are being extracted. Larger quantities must be defatted with petroleum ether before extracting) mycelial pads or dried culture material such as:

Solution A) Ammoniacal ethanol solution which is ethanol containing 4 % diluted ammonium hydroxide solution.

Solution B) 70 % acetone solution containing 2 % tartaric acid.

After the alkaloids are extracted with either of the previous solutions, the volatile solvents are then evaporated. The residue or aqueous solution is made alkaline (approx. pH 9) with ammonium hydroxide solution and then extracted with chloroform, ether, methylene chloride, or other appropriate solvent and evaporated to leave the ergot alkaloids in a free base form.

References: (Abou-Chaar 1961) (Amici 1969) (Ban'kovskii 1969) (Gröger 1961)

Preparation of Lysergic Acid

Ergot alkaloid (eg. 2 grams) can be transformed into lysergic acid when dissolved in (50 mL) normal methyl alcoholic potassium hydroxide solution and refluxed under nitrogen. A small amount of water (approx. 50 mL) is added and the alcohol is evaporated under reduced pressure. The base is extracted with ether and the aqueous layer is acidified with sulfuric acid to precipitate the crude lysergic acid, which is then purified.

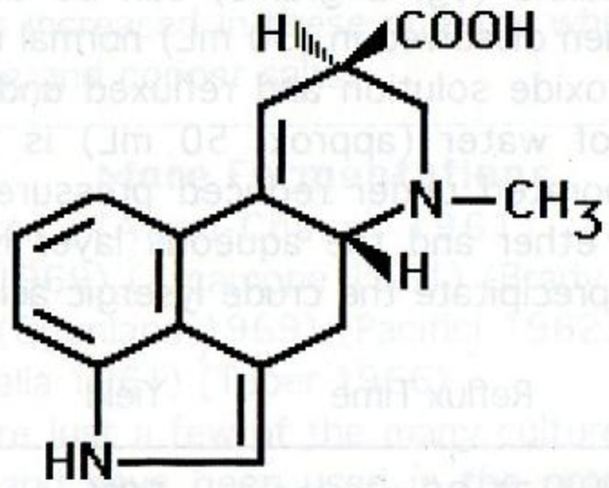
Alkaloid	Reflux Time	Yield	References
Ergine	75-80 minutes	80%	Jacob 1934
Ergometrine	135 minutes	75%	Smith 1932; 1936

Recrystallization of Lysergic Acid

Lysergic acid monohydrate crystallizes in very thin hexagonal leaflets when recrystallized from water. It decomposes at 238 degrees, but varies with rate of heating. Lysergic acid monohydrate, when dried (140 degrees at 2 mm.), forms anhydrous lysergic acid.
Reference: (Jacobs 1934)

Preparation of Lysergic Acid From Claviceps Culture

200 mL of fresh filtrates from *Claviceps* culture are mixed with 1.7 grams of potassium metabisulfate and 5 grams of active carbon. The mixture is stirred for 20 minutes and then the carbon is filtered off. The filtrate is washed with 40 mL water and then extracted with 250 mL of methanol containing 10 percent ammonia. The methanol extract is evaporated to leave a mixture of 25 % d-lysergic acid, 2 % d-iso-lysergic acid, 72 % 6-methyl-delta 8,9-ergoline-8-carboxylic acid and 1 % clavines.
Reference: (Schlientz 1967)



d-Lysergic Acid

CHAPTER ELEVEN:
FIELD INOCULATION OF RYE WITH CLAVICEPS PURPUREA

The field inoculation of rye with *Claviceps* can be achieved by using an artificial spore suspension similar to natural honey dew suspension. A sterilized solution of 34 to 66 percent beet sugar is most effective. Maple syrup, corn syrup and honey all proved ineffective.

Beet sugar solution (34 to 66 %) met all the following criteria of natural honey dew suspension. According to Ralph W. Lewis:

"**(1)** prevent immediate germination,

(2) protect the spores from death by desiccation after application, (spores remained viable for 5 days after the solution had been allowed to dry in air or over calcium chloride.)

(3) attract insects,

(4) allow germination once the spores come in contact with the pistils of the rye flowers."

Artificial Honey Dew-Preparation of Spore Suspension in Quart Canning Jars (Method by Hayes)

250 mL of wheat grain and 250 ml of water were poured in each quart canning jar and allowed to set overnight. The jars were sterilized by autoclaving for one hour at 15 lbs. Jars were inoculated with a sporulated (conidia) culture of *Claviceps* and allowed to grow at room temperature for six weeks. Cultures were then mixed with 500 mL of water and blended for two minutes. The cultures were screened through a 16 mesh and then a 40 mesh screen. To this is added one liter of beet sugar and stirred until dissolved.

Artificial honey dew suspension is stored at -18 to 0 degrees C. 1.75 quarts of suspension is produced from each quart of culture.

Spraying of the Rye Field

The rye flowers must be sprayed on a dry day as the solution will be washed off in the rain. The rye must also be sprayed when the rye flowers are in bloom. Rye flowers in 15 minute cycles every 45 minutes throughout the morning. Flowers begin opening when the sun first strikes the field until noontime. Weather and temperature also effects the flowering. The best time in which to spray occurs from 7 A.M. to 11 A.M.

In 1943, Ralph Lewis power sprayed his rye fields three times each morning for a period of three days. He used a 1:7 dilution of the suspension and 60% of the rye heads became infected with ergot.

According to Heinz G. Floss approximately 95 % of all peptide alkaloids are produced by extraction of field inoculated ergot.

Reference: (Lewis 1945; 1962)
Alkaloid extraction from ergot: (Arcamone 1961)
(Bankovskii 1969)

CHAPTER TWELVE: PREPARATION OF DIETHYLAMINE:

Journal of the Chemical Society (1916) 109: 174-175
by William Edward Garner and Daniel Tyrer

"A mixture of 8000 mL of ethanol and 3000 grams of ethyl bromide was saturated with ammonia several times during the day; the temperature of the mixture gradually rose to about 30 degrees C, and after some time the ammonium bromide began to crystallize out. After twenty-four hours the alcoholic ammonia solution was separated from the crystals of ammonium bromide, and the alcohol and unchanged ethyl bromide were distilled off. Water was added to the residue and the last traces of alcohol were removed by boiling. The hydrobromides of the mixed bases were then decomposed by a very concentrated solution of sodium hydroxide and the liberated amines distilled off. The alcoholic ammonia containing the ethyl bromide was used again for the preparation of more of the mixed hydrobromides. By using a fractionating column with ten bulbs there is no difficulty in obtaining an effective separation of the bases.

The yields were:	Monoethylamine.....	10.9 %
	Diethylamine.....	17.9 %
	Triethylamine.....	19.1 %

About 80 percent of the diethylamine (boiling within 1 degree) can be obtained by two fractional distillations. A further quantity of the mixed bases can be produced from the monoethylamine by treating it with more ethyl bromide.

Five hundred grams of crude monoethylamine (containing about 10 per cent of diethylamine) were dissolved in 2500 mL of alcohol and 1000 grams of ethyl bromide were added. The mixture must be cooled in ice, since much heat is evolved. After twenty-four hours 200 grams of ammonium bromide were added to fix any free bases, and the solution was treated as described above.

The yields were:	Monoethylamine.....	38.7 %
	Diethylamine.....	30.1 %
	Triethylamine.....	17.3 %

As the monoethylamine can be again used for the preparation of diethylamine, about 50 percent of the monoethylamine can be converted into diethylamine."

PREPARATION OF ETHYLAMINE AND DIETHYLAMINE

Journal of the Chemical Society (1918) 113: 900-901
by Emil Alphonse Werner

"Five liters of 90 percent ethanol were saturated with ammonia (compare this volume p. 698) until 490 grams of the gas had been dissolved, 200 grams of ethyl bromide were added (ratio ethyl bromide to ammonia approximately 1 to 16), after which, at successive intervals of two days, fresh quantities of the alkyl haloid were added in the following amounts: 180, 170, 150, 130, 110, 100, 80, and, finally, 66 grams. Preliminary experiments had shown that with the above ratio of ammonia the whole of the ethyl bromide was decomposed after two days, hence the successive quantities were regulated so as to maintain the desired excess of ammonia throughout the progress of the change. In all, 1186 grams of ethyl bromide were used; ammonium bromide began to separate on the twelfth day, and on the sixteenth day the preparation was stopped.

Test experiments on a small scale with pure alcohol had shown that when ammonium bromide separated in quantity in the early stage of the process, the formation of triethylamine was promoted when the reaction was prolonged. The reason is fairly obvious when the probable mechanism of the process is considered, hence it was found advantageous to use alcohol containing 10 percent water.

The alcoholic solution, separated from ammonium bromide, was concentrated by distillation (the ammonia evolved was used to charge more alcohol) until nearly all the ammonium bromide formed had separated, 362 grams of which were recovered.

The solution of the hydrobromides of the mixed amines was distilled until the temperature reached 130 degrees C, in order to remove the last traces of alcohol. Where it was not found convenient to liberate the entire quantity of the mixed

amines by the addition of aqueous sodium hydroxide to the residue, chloroform was used as a solvent for their separation.

Ethylammonium bromide is dissolved by chloroform to the extent of only 0.163 gram in 100 mL at 14 degrees C, whilst the same volume of chloroform dissolves 42 grams of diethylammonium bromide. By this means, 465 grams of pure ethylammonium bromide and 510 grams of diethylammonium bromide, containing slightly more than 5 percent of triethylammonium bromide, were obtained. After the separation of triethylamine (14 grams) by treatment with the requisite proportion of sodium hydroxide, 226 grams of diethylamine, collected at 56-57.5 degrees C and dried over potassium hydroxide were obtained."

Amines can be produced by many different chemical syntheses, so numerous that I will list only a few references. A thorough search of German, Russian, and American scientific literature is waiting should the reader wish to look into it further.
References: (Davies 1952) (Lemon 1962) (Price 1916) (Rakshit 1913) (Watt 1947)

PREPARATION OF ETHYL BROMIDE (1-BROMOETHANE) FROM SODIUM BROMIDE AND ETHYL ALCOHOL

$$H_2SO_4 + NaBr \rightarrow HBr + NaHSO_4$$

$$C_2H_5OH + HBr \rightarrow C_2H_5Br + H_2O$$

270 mL of water is poured into a one liter boiling flask equipped with a long condenser set downward for distillation. 300 Grams of finely powdered (ground into a fine powder in a mortar and pestle) sodium bromide are added with stirring. 110 mL of ethanol are added and then 400 grams (218 mL) of concentrated sulfuric acid are gradually added through a dropping funnel. The mixture is not refluxed but is slowly distilled. The end of the condenser is equipped with a adaptor tube that is very slightly immersed in a beaker of ice water. The distillate is collected in the ice water. The water insoluble layer contains the ethyl bromide. It is separated from the water and washed with water.

Purification

The crude ethyl bromide can be purified by washing with 60 grams of cold concentrated sulfuric acid and then washed (dried) with a sodium carbonate solution (15 grams of sodium carbonate in 150 mL of water). Ethyl bromide can be further purified by distilling at 38.5-39.5 degrees C. Boiling chips (porous plate chips) must be added to the boiling flask to prevent superheating and bumping. Yields are 90 to 95 % theoretical.

References: (Kamm 1941) (Vogel 1943)

CHAPTER THIRTEEN: HYDRAZINE

Hydrazine (anhydrous) has many applications in organic chemistry, and is used in rocket fuels.

CAUTION! HYDRAZINE AND AMMONIA ARE BOTH VIOLENT POISONS! BOTH CAN CAUSE SEVERE LUNG IRRITATION, LIVER AND KIDNEY DAMAGE WHICH DOES NOT APPEAR FOR DAYS.

$$2NH_3 + NaOCl \rightarrow NH_2NH_2 + H_2O + NaCl$$

$$NH_2NH_2 + H_2SO_4 \rightarrow NH_2NH_2H_2SO_4$$

$$NH_2NH_2H_2SO_4 + NH_3 \rightarrow NH_2NH_2$$

HYDRAZINE SULFATE

A large Pyrex® pie dish is poured a solution of 900 mL of strong ammonia water, 600 mL of distilled water, 225 mL of 10 % gelatin solution and 800 mL of a normal solution of sodium hypochlorite. The solution is heated as rapidly as possible until it boils down to 1/3 the original volume. The solution is then cooled with ice and suction filtered through two layers of towels and then through ordinary filter paper.

The solution is placed in a beaker and cooled to 0 degrees in an ice/salt bath. 10 mL of concentrated sulfuric acid per 100 mL of solution is gradually added with rapid stirring. The solution is allowed to cool for several hours. Hydrazine sulfate precipitates and is suction filtered from the solution and washed with alcohol. The yield is 35 to 38 grams of hydrazine sulfate.

Hydrazine sulfate should be white crystals. If the crystals are not pure white they should be purified. 50 mL of boiling

water are mixed with 10.5 grams of impure crystals and filtered through animal charcoal. The solution is then cooled to 0 degrees in an ice/salt bath for several hours. Hydrazine sulfate precipitates and is filtered from the solution.

ANHYDROUS HYDRAZINE

Anhydrous hydrazine can be obtained from hydrazine salts by various procedures. The most simplified involves the use of liquid ammonia and two thermos bottles.

Liquid ammonia can be obtained by condensing ammonia gas (using a dry ice cold trap) into liquid ammonia.

The liquid ammonia is poured into a thermos bottle. 50 Grams of hydrazine sulfate are gradually added with rapid stirring (mechanical). The solution is stirred for another half hour after addition is complete. The solution is filtered rapidly through a fluted filter paper, any remaining solids are transferred back to the original thermos bottle and liquid ammonia is added and then run through the fluted filter paper again. The combined solutions of liquid ammonia containing anhydrous hydrazine are evaporated to leave colorless (90 plus %) anhydrous hydrazine. The yield is 6 to 8 grams of anhydrous hydrazine.

Anhydrous hydrazine must be stored in a tightly sealed amber bottle. It will remain viable for many years if stored in a cool dark place.

Refs.: (Adams 1941) (Barber 1948) (Brown 1911) (Elgin 1929) (Friedrichs 1913) (Hurd 1929) (Organic Syntheses (1941) 21: 70)(Organic Syntheses 24: 53-55) (Organic Syntheses Col. (2): 86) (Penneman 1949) (Raschig 1927) (Schenk, P.W.; in Handbook of Preparative Inorganic Chemistry (1) 469-472) (Troyan 1953) (Wenner 1932)

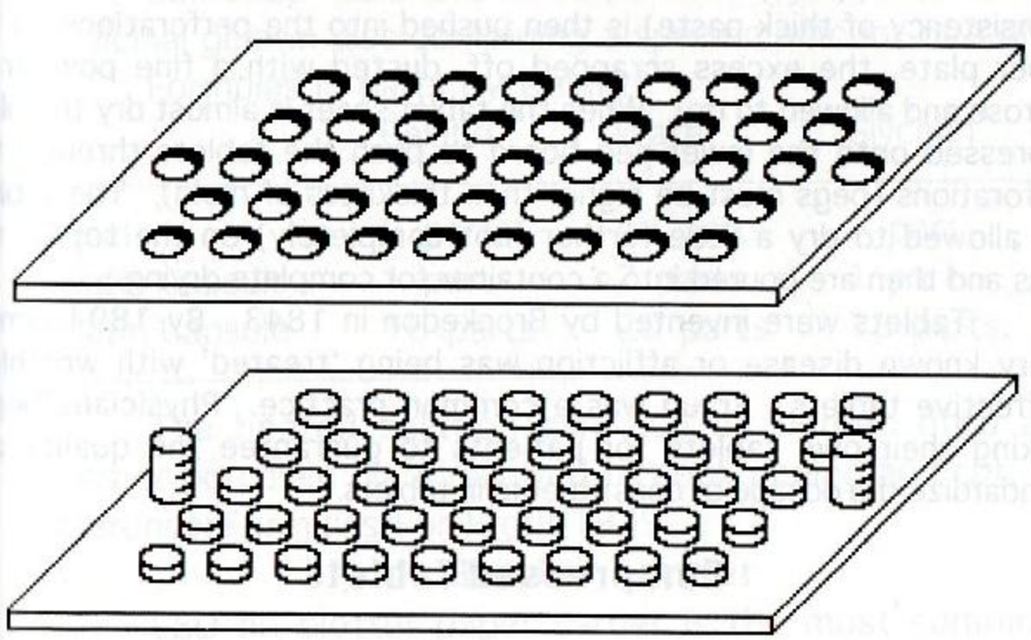
CHAPTER FOURTEEN: TABLET MANUFACTURE

LSD has been dispersed in numerous forms. Delysid (LSD-25) from Sandoz was distributed in ampules and also tablets containing 100 μg.. LSD that appeared outside of research circles was usually titrated (dosed) on sugar cubes and in tablet form (both as compressed tablets and molded tablets) of many sizes and colors. LSD that is dispersed into films (clearlight, window pane) of gelatin, agarose or cellulose also appears in a variety of colors and shapes. The most common form of LSD appears in blotter paper form.

During the nineteen sixties dosages of LSD were extremely high (e.g. 500 μg. Owls, sugar cubes). Today the blotter form (which is most prevalent) of LSD ranges from approximately 35 to 75 μg.

The shape, color and dosage are the trademark of the laboratory.

Molded Tablets (Tablet Triturates)



Tablet Triturate Machine

Tablets can be molded using a mixture of sucrose, lactose and/or dextrose. A predetermined amount of active ingredient is mixed with a pre-weighed amount of tablet mixture. This mixture is pushed onto the upper plate mold and tablets are ejected from the mold by gently pressing it onto the pegboard and allowed to dry.

The hardness of a tablet is manipulated by adjusting the constituent proportions of sugars. Two forms of these tablets can be made; one is called a hypodermic tablet, it easily dissolves in water and is not a hard tablet. These types of tablets break down (mechanically) very easily during storage and transport. The second type is harder and retains its shape in transport. A general formula for hard tablets appears in Remington's Practice of Pharmacy: five parts lactose to one part sucrose. The composition is moistened with 70 % alcohol and mixed thoroughly.

When the mixture is moistened too much the consistency is too liquid to form tablets; the tablets come out looking like a blob of gooey dough. If the mixture is not moistened enough the tablets will crack and fall apart.

Trituration of Tablets

The upper plate is placed on flat surface. The mixture (consistency of thick paste) is then pushed into the perforations on the upper plate, the excess scrapped off, dusted with a fine powder of sucrose and allowed to dry. When the tablet sheet is almost dry the plate is pressed onto the lower peg board to push the tablets through the perforations (pegs must be higher then thickness of mold). The tablets are allowed to dry a little further (not completely) on the top of the pegs and then are poured into a container for complete drying.

Tablets were invented by Brockedon in 1843. By 1894 almost every known disease or affliction was being 'treated' with worthless ineffective tablets. Fraud was a common practice. Physicians began making their own tablets for patients to guarantee the quality and standardize the dosage of constituents in tablets.

Compressed Tablets

Compressed tablets are formed with a tablet machine. The LSD is diluted into sugar, binder and lubricants and "punched" into tablets. LSD in this form was most prevalent during the 1960's thru 1980's. The cost of tablet equipment, size and weight (tonnage) tends to make this form prohibitive for security reasons. Tablets take up space and can not be easily concealed. Transportation of large quantities of tablets is subject to discovery by law enforcement.

Thin Film Carrier: "Clearlight"

Clearlight, also called window pane, has appeared in a carrier of small film pyramids (many colors). This form was achieved by spraying a mixture of LSD/jelling agent on to plastic light covers of small pyramids. Small film squares have appeared containing 225 μg. of LSD (mid 1970's).

Preparation of Clearlight Carrier: "Sheeting"

Clearlight is formed by several different ways. A mixture of an appropriate solvent, with a jelling agent (more jelling agent makes sheets more flexible) is heated. LSD in solution is thoroughly mixed with the jelling mixture and then sprayed on plastic molds or sheeted using a apparatus that makes thin layer films for chromatography applications. The individual doses are cut using a paper cutter or agarose film cutter.

Lamellae also called lamels or eye discs is a small medicinal gelatin disc containing a specific amount of a drug.

Formulas in parts by weight:

	Gelatin	Water	Glycerin
Lamel	9 parts	44 parts	1 part
Gelatin Capsule	1 part	2 parts	1 part.
Gelatin Capsule	16 parts	20 parts	15 parts.

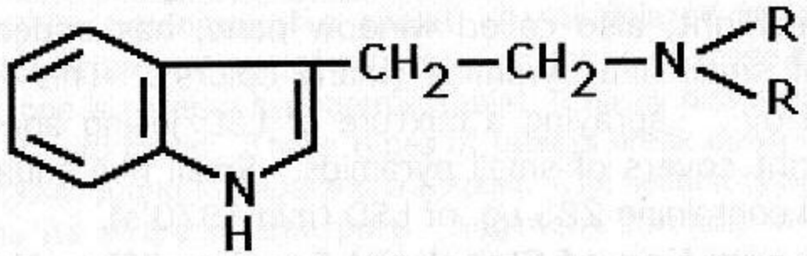
The heated solution can also be poured onto a waxed glass or porcelain plate, allowed to cool, peeled and cut.

Reference: Formulas For Profit 1939

Blotter Carrier

LSD on blotter paper carrier is the most common form. The blotter paper is perforated in squares and printed with symbols, cartoon characters and designs. A predetermined amount of LSD is dissolved into a solvent and blotter paper is soaked to absorb a titrated amount of LSD. It is the easiest form of LSD for transportation, but will break down (if not protected) on exposure to heat, light and air.

CHAPTER FIFTEEN: N,N-DIALKYL-TRYPTAMINES

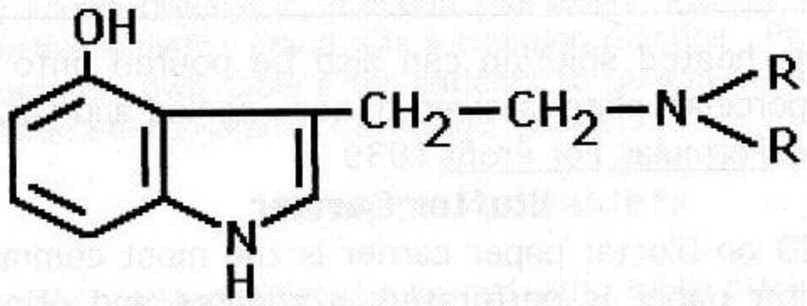


N,N-Dialkyltryptamine

Chemical Name	Abbreviated Name	Alkyl Chain
N,N-Dimethyltryptamine	N,N-DMT	R=CH_3
N,N-Diethyltryptamine	N,N-DET	R=CH_2CH_3
N,N-Dipropytryptamine	N,N-DPT	R=$CH_2CH_2CH_3$

Longer N,N-dialkyl chain substitutions are non-hallucinogenic, and the duration of activity increases. The psychoactive effects have been reported to produce states which are conducive to meditation.

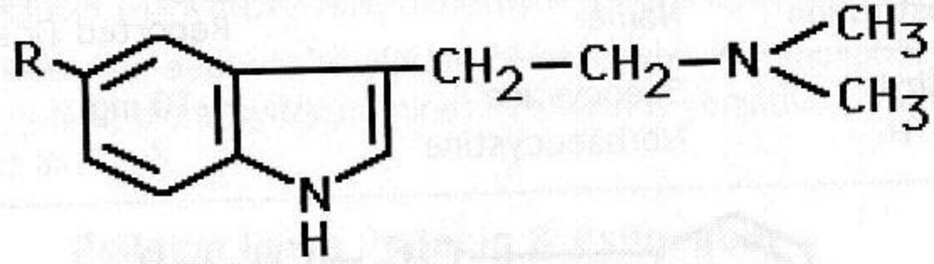
N,N-DMT is a naturally occuring alkaloid of many members of the legume family (Fish 1955) (Ghosal 1966) (Iacobucci 1964) (Pachter 1959) and also occurs as an endogenous neurochemical in the brain (Christian 1976; 1977). N,N-DMT is a hallucinogen. N,N-DPT is non-hallucinogenic, has been used in psychotherapy (Soskin 1973) and in terminal patients (Richards 1978).



4-Hydroxy-N,N-Dialkyltryptamine

Substitution	Abbreviated Names		Reported Dosage
N,N-Dimethyl	4-OH-N,N-DMT	CX-59	7-10 mg.
N,N-Diethyl	4-OH-N,N-DET	CZ-74	15-20 mgs.

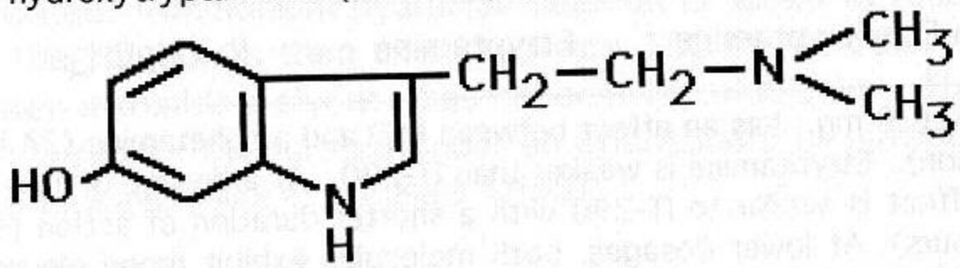
4-Hydroxy-N,N-dimethyltryptamine is commonly called psilocin. Psilocin and psilocybin (O-phosphoryl-4-hydroxy-N,N,-dimethyl-tryptamine) have been found in some species of mushrooms (Benedict 1967) (Repke 1977), most notably in *Psilocybe* (Benedict 1962) (Tyler 1961), but have also been found in some *Gymnopilus* species (Buck 1967) (Hatfield 1968; 1971; 1978) also called Big Laughing Gems (Sanford 1971). *Psilocybe* mushrooms are also called Sacred Mushrooms, Teonanácatl (God's Flesh), by those who revere these mushrooms as the true holy sacrament and Eucarist (Singer 1958). Psilocybin can also be produced synthetically (Hofmann 1963).



5-Substituted-N,N-Dialkyltryptamine

Substitution	Abbreviated Name	Reported Dosage
5-Hydroxy	5-OH-N,N-DMT	Not psychoactive
5-Methoxy	5-Meo-N,N-DMT	6-10 mg.

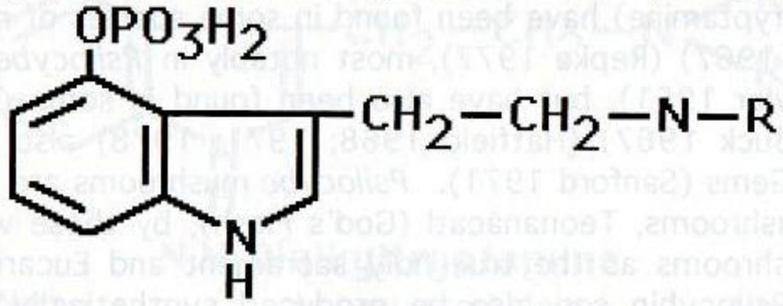
Bufotenin (5-Hydroxy-N,N-dimethyltryptamine) is a constituent of toad venom (Lyttle 1993) and various legumes. Synthetic preparation of 5-hydroxytryptamines (Ek 1953) (Justoni 1960) (Speeter 1955).



6-Hydroxy-N,N-Dimethyltryptamine

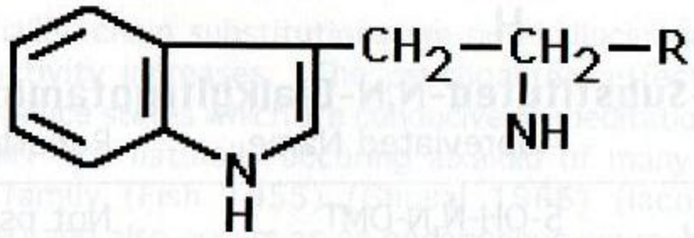
6-Hydroxy-DMT is the naturally occuring urinary metabolite of endogenous N,N-DMT (Szára 1962). See also (Rosenburg 1963). All readers should read TIHKAL for a more extensive review of homologs.

5-Methoxy-N-methyltryptamine from reed canary grass: (Wilkinson 1958). Tryptamine from *Petalostylis labicheoides*: (Johns 1966)



o-Phosphoryl-4-hydroxy-N-Alkyl-tryptamine

R Substitution	Name	Reported Dosage
N-Methyl	Baeocystine	4-10 mg.
H	Norbaeocystine	?

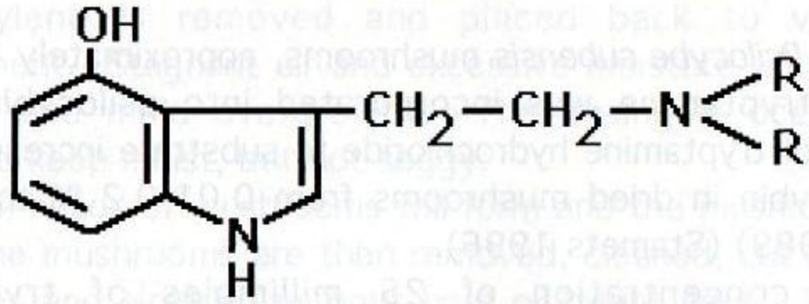


alpha-Alkyltryptamine

Chemical Name	Abbreviated Name	Substitution
alpha-Methyltryptamine	IT-290	R=CH_3
alpha-Ethyltryptamine	Etryptamine	R=CH_2CH_3

IT-290 (20 mg.) has an effect between LSD and amphetamine (24 hour duration). Etryptamine is weaker than IT-290. At a dosage of 120 mg. the effect is similar to IT-290 with a shorter duration of action (6 to 12 hours). At lower dosages, both molecules exhibit mood elevation effect possibly due to MAOI. Refs.: (Glennon 1993) (Hollister 1960) (Huang 1991) (Jacob 1994) (Kalir 1962) (Krebsk 1993) (Murphree 1961) (Repke 1985) (Szára 1962). Many of the hydroxytryptamines are neurotoxic, see Serotonin Neurotoxins (1978); The Serotonin Receptor (1988).

CHAPTER SIXTEEN: PSILOCIN



Psilocin (4-hydroxy-N,N,-dimethyltryptamine) (R = CH_3) is formed from the dephosphorylation of psilocybin (O-phosphoryl-4-hydroxy-N,N,-dimethyltryptamine). Psilocin is sensitive to light, heat and air.

Psilocin From Psilocin & Psilocybin Containing Mushrooms

20 Grams of dried psilocybin containing mushrooms are ground into powder. The powder is mixed with 150 mL of dilute acetic acid. Glacial acid acid is added to adjust solution to pH 4. The solution is then heated on a boiling water bath until the temperature of the solution reaches 70 degrees (approximately 10 minutes). The solution is then suction filtered and concentrated. Ammonium hydroxide solution is added to reach pH 8. The solution is then extracted with 150 mL of ether or any water insoluble solvent that psilocin is soluble in. The solution is rapidly evaporated under an atmosphere of nitrogen or argon to leave psilocin. (Casale 1985)

Yields vary with species, but this extraction is is capable of extracting psilocin suitable for forensic analysis (gas chromatography, IF spec.). The extract can be further purified by crystallization (eg. methanol).

Increasing Psilocybin & Psilocin Content of Cultivated Carpophores Using Tryptamine

In *Psilocybe cubensis* mushrooms, approximately 22 % of labeled tryptamine was incorporated into psilocybin. The addition of tryptamine hydrochloride to substrate increases yield of psilocybin in dried mushrooms from 0.01-0.2 % to 3.3 %. (Gartz 1989) (Stamets 1996).

A concentration of 25 millimoles of tryptamine hydrochloride is added to 10 grams mushroom substrate (spawn media). The substrate is composed of either rye grain spawn or rice spawn. The following spawns can be used for the culture of many species of mushrooms.

Rye Grain Spawn: 50 grams of rye grain
65 mL of water

Cow manure/Rice spawn: 0.5 cup of dried cow manure
0.25 cup of rice grain
1.5 cups of water

The spawn is placed in one pint wide mouth canning jars and pressure cooked for 30 minutes. A culture grown on PDA or MEA media is inoculated into the spawn jars and allowed to grow until the jar is completely covered in mycelium. A large aquarium can be used to cultivate the mushrooms for identification.

A large aquarium is half filled with water. A water circulator is used as stagnant water will contaminate cultures. A casserole dish is floated in the aquarium and filled with spawn. 1/3 volume of straw (not hay) is thoroughly mixed with broken up spawn and poured into the casserole dish. Manure/rice spawn need not be cased. Rye grain spawn must be cased. Casing is made by saturating 1.5 cups of peat moss with water, to this is added and mixed, 1 cup of vermiculite, & 1/4 to 1 cup of calcium carbonate. The casing is added to a depth of one inch.

The aquarium is covered with a piece of polyethylene to keep moisture constant. Three or four times a day the polyethylene is removed and placed back to vent the environment. Stagnant air and excessive moisture will promote bacteria and mold overgrowth. The casing is occasionally misted to keep moist, but not soggy.

Pin heads of mushrooms will form and the mushrooms will fruit. The mushrooms are then removed, cleaned, cut into very thin slices and air dried without heat or bright light. The dried mushroom pieces may then be extracted for forensic analysis to determine constituents.

For the mycologist, LBNs (little brown mushrooms) are not easily identified by microscopic means. Many new species of mushrooms have been overlooked, because of their small size and diversity. These mushrooms are a challenge for the mycologist, but are not of interest to those looking to produce psychotropic substances. When a mycologist is cultivating such unknown species it is best to sterilize casing and water used in misting. References: (Hofmann 1959) (San Antonio 1971) How to Identify and Grow Psilocybin Mushrooms; Stevens & Gee The Mushroom Cultivator; Stamets & Chilton

Psilocin canbe used to produce psilocybin (O-phosphoryl-4-hydroxy-N,N,-dimethyltryptamine) (Hofmann 1963). Psilocin (4-hydroxy-N,N-dimethyltryptamine) can be produced in small amounts (along with other hydroxy-DMT molecules) from the oxidation of N,N-DMT. See: (Eich 1966) (Julia 1969; 1972).

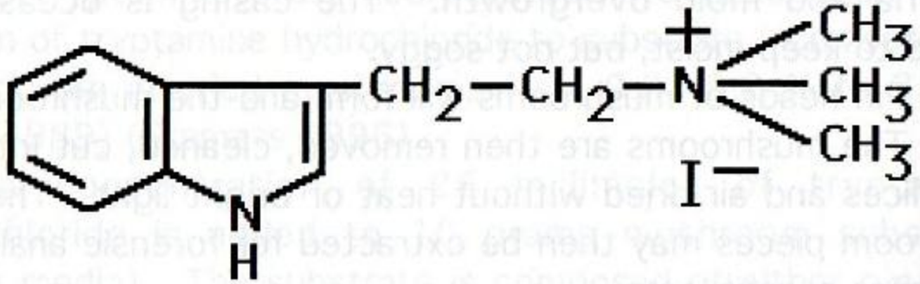
Other oxidation reactions maybe useful in gaining a better understanding of biochemical mechanisms involved in the endogenous production of neurotransmitters (Arnow 1942) (Broodie 1954) (Dalgliesh) (La Du 1955) (Raper 1932) (Udenfriend 1954).

5-Hydroxytryptophan from tryptophan (Renson 1961).

Psilocybin has also been obtained by the submerged culture of *Psilocybe* species (Catalfomo 1964) (Leung 1969).

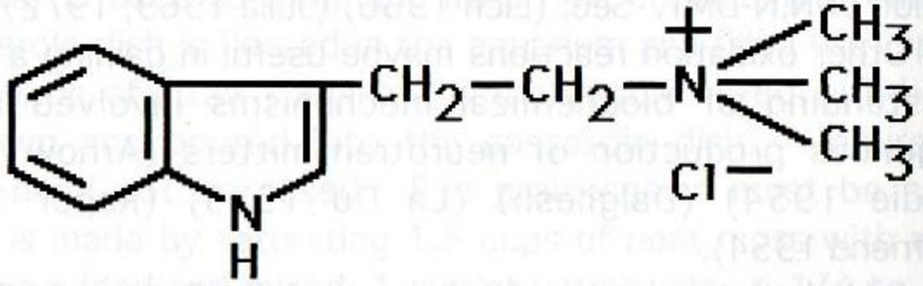
CHAPTER SEVENTEEN:

Preparation of Phenyl Ring Substituted NN-Dialkyltryptamines



Preparation of Trimethyl-ß-3-indolylethyl-ammonium iodide

1.6 Grams of tryptamine (0.01 moles) is mixed in 36 mL anhydrous alcohol. 6 Grams of methyl iodide containing 5.4 grams of anhydrous sodium carbonate are added to the solution and refluxed on a hot water water bath for 5 hours. The hot solution is then rapidly suction filtered. Alcohol is added to the residue and heated to boiling and rapidly suction filtered. The filtrate is concentrated under reduced pressure. Large colorless needles of trimethyl-ß-3-indolyl-ethyl-ammonium iodide precipitate and are suction filtered. The solution is reduced further to crystallize more trimethyl-ß-3-indolyl-ethyl-ammonium iodide.



Trimethyl-ß-3-indolylethyl-ammonium chloride

Preparation of Trimethyl-ß-3-indolylethyl-ammonium chloride From Trimethyl-ß-3-indolyl-ethyl-ammonium iodide

0.05 Mole of trimethyl-ß-3-indolyl-ethyl-ammonium iodide, is mixed in 25 mL of absolute alcohol. The solution is refluxed for 3 hours with 7.2 grams of silver chloride. The hot solution is rapidly filtered. The residue is mixed with anhydrous alcohol, boiled and filtered again. The solutions are evaporated under reduced pressure and allowed to set for 24 hours. Large colorless crystals of trimethyl-ß-3-indolyl-ethyl-ammonium chloride precipitate and are collected by vacuum filtration.

Preparation of N,N-Dimethyltryptamine from Trimethyl-ß-3-indolyl-ethyl-ammonium chloride

Trimethyl-ß-3-indolyl-ethyl-ammonium chloride is heated to 245-250 degrees C. in a vacuum. N,N-Dimethyl-tryptamine distills with foaming leaving a red-brown substance in the boiling flask.

Starting Molecule: 5-Methoxytryptamine
Product: 5-Methoxy-N,N-dimethyltryptamine
Reference: (Hoshino 1936) (Wieland 1934)

Starting Molecule: 5-Methoxytryptamine
Product: 5-Methoxy-trimethyl-ß-3-indolyl-ethyl-ammonium iodide
Reference: (Wieland 1934)

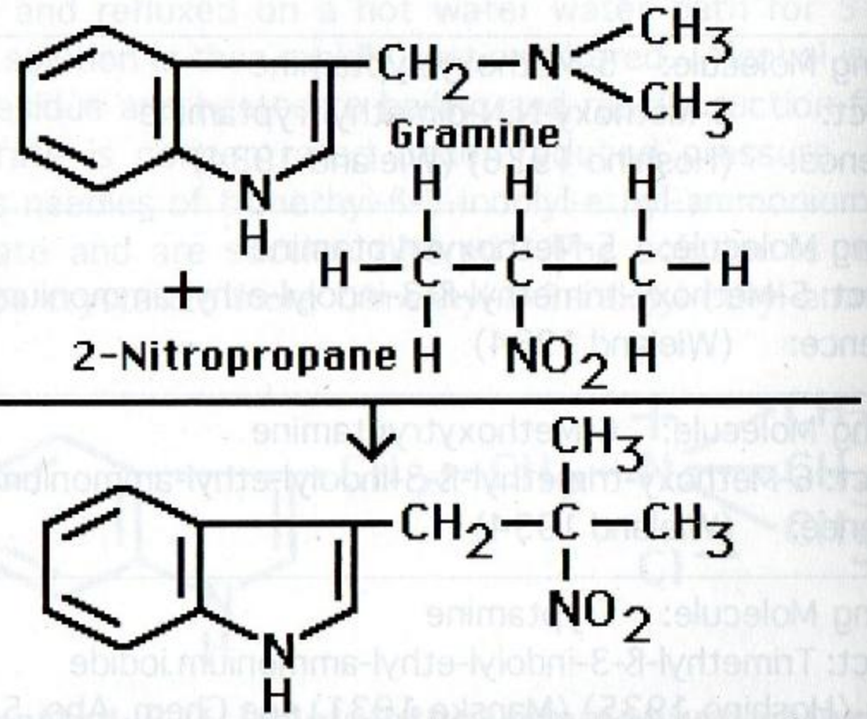
Starting Molecule: 6-Methoxytryptamine
Product: 6-Methoxy-trimethyl-ß-3-indolyl-ethyl-ammonium iodide
Reference: (Wieland 1934)

Starting Molecule: Tryptamine
Product: Trimethyl-ß-3-indolyl-ethyl-ammonium iodide
Refs.: (Hoshino 1935) (Manske 1931) see Chem. Abs. 52: 14083

Preparation of Tryptamine From Tryptophan
The Decarboxylation of Tryptophan by Thermal Splitting

Tryptophan is placed in a distillation apparatus. A vacuum is applied and the boiling flask is gradually heated. At approximately 300-325 degrees the tryptophan begins to melt as the carbon dioxide is split from the molecule. A distillate comes over. The distillate is redistilled under reduced pressure. The yellow resinous substance smells like skatole and is dissolved in ether. The ether solution is concentrated under reduced pressure to crystallize the tryptamine.

Starting Molecule: N-Methyl-L-tryptophan
Product: N-Methyl-tryptamine
Reference: (Hoshino 1935)



Preparation of 3-(alpha, alpha-Dimethyl-alpha-nitroethyl)indole

Phenyl ring substituted 3-aminomethylindoles, 3-(N,N-dimethyl)aminomethylindoles; (e.g. gramine), and 3-(N-alkyl and N,N-dialkyl)-aminomethylindoles can be used in the following reaction to produce the alpha substitued nitroethylindoles. Substitutions on the phenyl ring (e.g. 4-methoxy) can be used, but hydroxy groups must be protected (e.g. methoxy instead of hydroxy groups).

17.4 Grams (0.1 mole) of gramine is mixed with 150 mL of 2-nitropropane. 7.8 Grams (0.2 mole) of sodium hydroxide is added. The mixture is refluxed for 8 hours (until evolution of dimethylamine stops) as a slow stream of nitrogen is run through the mixture. The solution was cooled. 75 mL of 10 % acetic acid is added and extracted with 300 ml of ether. The ether layer is repeatedly washed with water and dried over Epsom salts. The ether solution is clarified with diatomaceous earth, filtered, and the ether evaporated to leave a residue of 3-(alpha, alpha-dimethyl-alpha-nitroethyl)indole (approximately 70 % yield).

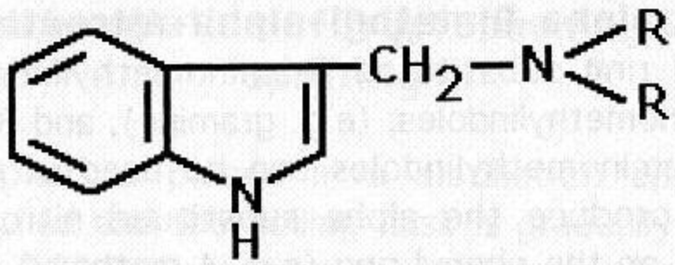
Starting Mol.: 5-Benzyloxygramine Reagent: 2-Nitropropane
Prdt.: 5-Benzyloxy-3-(alpha, alpha-dimethyl-alpha-nitroethyl)-indole Reference: (Heizelman 1960)

3-(alpha, alpha-Dimethyl-alpha-nitroethyl)indole can be reduced to produce alpha-methyl-tryptamine.

ELECTROLYTIC REDUCTION OF 3-(2-NITRO-VINYL)INDOLE TO PREPARE TRYTAMINE

Starting Molecule: 3-(2-Nitro-vinyl)indole
Product: Tryptamine Reference: (Kametani 1961)
See electrolytic reduction apparatus as described in Amphetamine Syntheses.

SYNTHESES OF GRAMINE ANALOGS



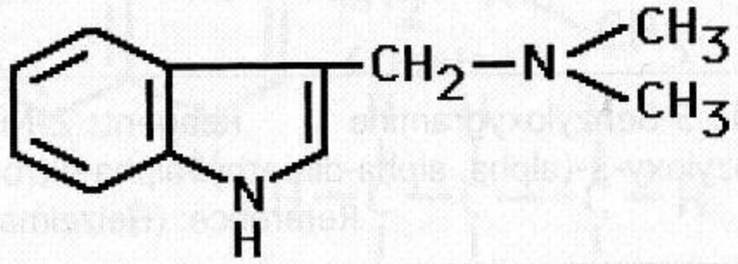
Condensations of Indoles with Aldehydes and Secondary Amines

Substituted indoles may be used, but must be protected (e.g. methoxy instead of hydroxy). Substitutions on the phenyl ring will result in the formation of substituted 3-(dialkylamino-methyl)-indoles such as 4-methoxy-gramine.

Replacement of dimethylamine with equal molar amounts of diethylamine, dipropylamine will result in the formation of N,N-substituted 3-(dialkylaminomethyl)indoles.

When equal molar amounts of reagents are used the yields are almost theoretical.

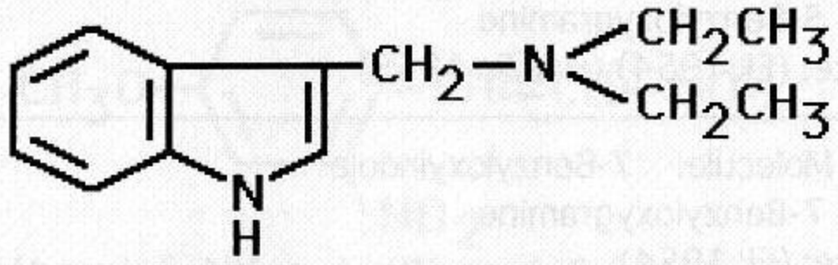
Preparation of 3-(Dimethylaminomethyl)indole



3-(Dimethylaminomethyl)indole (Gramine)

All the following are cooled in an ice bath. 12.33 grams of aqueous dimethylamine solution (53%) and 20 mL of glacial acetic acid, are mixed with 11 grams of formaldehyde solution (37 %). 16.8 Grams of indole is added. An exothermic reaction results as the indole dissolves. After several hours the solution is made alkaline with dilute sodium hydroxide solution. The mass crystallizes and is suction filtered, washed with water and dried over potassium hydroxide. Approximately 25 Grams of white gramine crystals are obtained. This can be further purified by crystallizing from acetone.

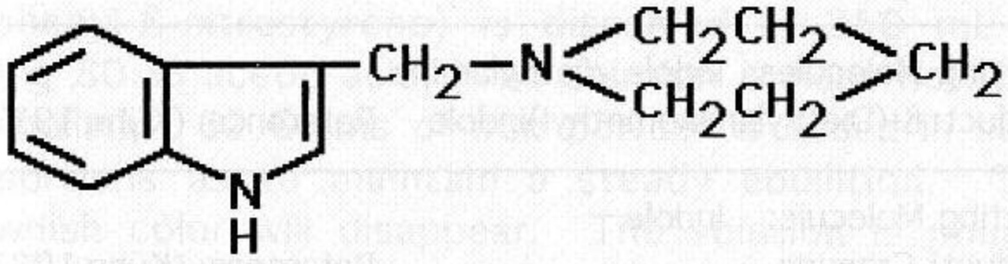
Preparation of 3-(Diethylaminomethyl)indole



3-(Diethylaminomethyl)indole

10 Grams of diethylamine hydrochloride are mixed with 7.4 grams of sodium acetate. The mixture is then dissolved in 35 mL of water. A solution of 10 grams of indole with 7.2 grams of formaldehyde solution (37 %) is then added. The mixture is placed in a refrigerator for several days to crystallize the 3-(diethylaminomethyl)indole. Approximately 15 grams of crude 3-(diethylaminomethyl)indole are obtained. Indole is extracted from the crude 3-(diethylamino-methyl)-indole leaving a pure crystalline mass of approximately 12.25 grams.

Preparation of 3-(N-Piperidylmethyl)indole



ß-(N-Piperidylmethyl)indole

At room temperature, 7 grams of indole, 5 grams of piperidine and 4.8 grams of 37 % formaldehyde solution are combined. An exothermic reaction results and is allowed to stand for several hours, diluted with water and extracted with ether. The ether solution is dried and evaporated to leave an oil which is placed into the refrigerator to crystallize. Approximately 12 grams of the crude ß-(N-piperidyl-methyl)indole are obtained which can be purified by crystallization in dilute methanol.

Starting Molecule: 5-Benzyloxyindole
Product: 5-Benzyloxygramine
Reference: (Ek 1954) (Hamlin 1955)

Starting Molecule: 7-Benzyloxyindole
Product: 7-Benzyloxygramine
Reference: (Ek 1954)

Starting Molecule: 5-Benzyloxy-2-methylindole
Product: 5-Benzyloxy-2-methylgramine Ref.: (Heizelman 1960)

Starting Molecule: 6-Benzyloxy-5-methoxyindole
Product: 6-Benzyloxy-5-methoxygramine Ref.: (Taborsky 1965)

Starting Molecule: 5-Bromoindole
Product: 5-Bromogramine Reference:(Snyder 1948)

Starting Molecule: 4-Chloroindole
Product: 4-Chlorogramine Reference: (Fox 1951)

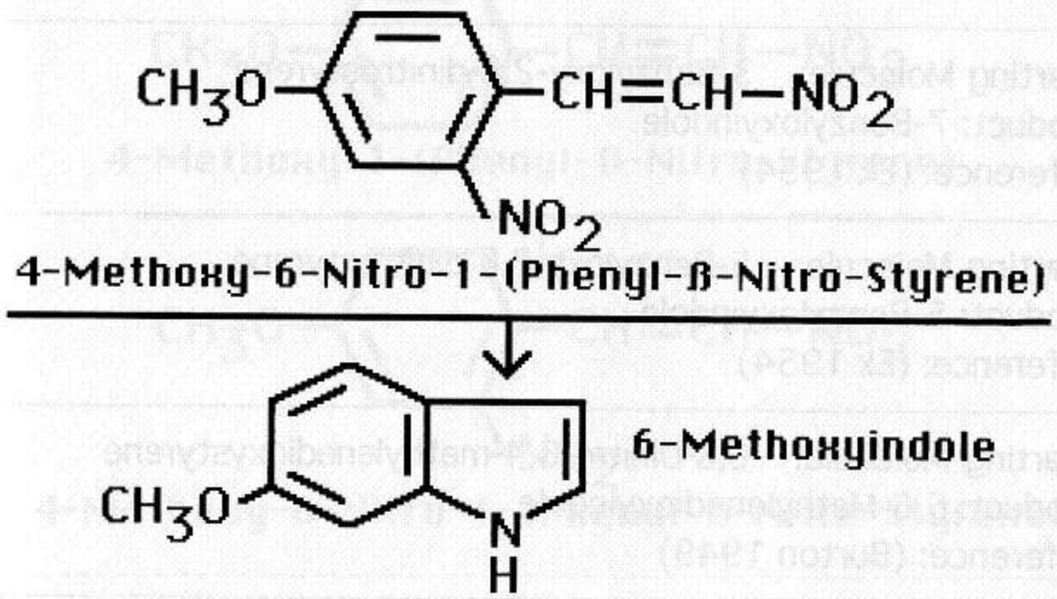
Starting Molecules: Indole, diethylamine
Product: ß-(Diethylaminomethyl)indole Reference: (Kühn 1937)

Starting Molecule: Indole
Product: Gramine Reference: (Kühn 1937)

Starting Molecules: Indole, piperidine
Product: ß-(N-Piperidylmethyl)indole Reference: (Kühn 1937)

Starting Molecule: 1-Methylindole
Product: 1-Methylgramine Reference:(Snyder 1948)

Starting Molecule: 5-Methoxyindole
Product: 5-Methoxygramine Reference: (Cook 1951)



Preparation of 6-Methoxyindole
From 4-Methoxy-6-Nitro-1-(Phenyl-ß-nitrostyrene)

Ten grams (0.052 moles) of 4-methoxy-6-nitro-1-(phenyl-ß-nitrostyrene) is dissolved in 250 mL of boiling 80 % acetic acid. The solution is kept hot, but not boiling. 62 Grams of iron powder is added in such proportions as to maintain a steady ebullition. The brownish color will disappear. The solution is poured into a large separatory funnel and mixed with an aqueous solution of 300 grams of sodium hydrosulfite in 1.5 liters of water. The solution is neutralized with sodium bicarbonate and the shaken. The mixture is extracted with ether or ethyl acetate. The extract is dried with sodium sulfate and evaporated to leave a gum. The gum is extracted with petroleum ether (b.p. 40-60) and evaporated to crystallize colorless needles of 6-methoxy-indole.

Starting Molecule: 3-Benzyloxy-2,ß-dinitrostyrene
Product: 7-Benzyloxyindole
Reference: (Ek 1954)

Starting Molecule: 5-Benzyloxy-2,ß-dinitrostyrene
Product: 5-Benzyloxyindole
Reference: (Ek 1954)

Starting Molecule: 6,ß-Dinitro-3,4-methylenedioxystyrene
Product: 5,6-Methylenedioxyindole
Reference: (Burton 1949)

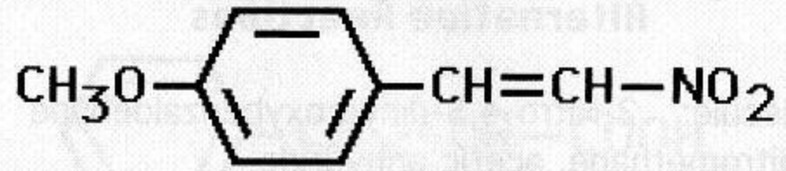
Starting Molecule: 2,ß-Dinitro-6-acetoxystyrene
Product: 4-Hydroxyindole
Reference: (Beer 1948)

Starting Mol.: 3-Hydroxy-4-methoxy-ß-2-dinitrostyrene
Product: 7-Hydroxy-6-methoxy-indole
Reference: (Beer 1951)

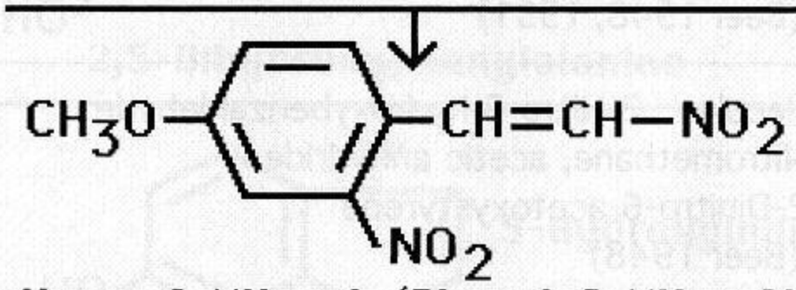
Starting Mol.: 3-Hydroxy-4-methoxy-ß-methyl-ß-2-dinitrostyrene
Product: 7-Hydroxy-6-methoxy-2-methylindole
Reference: (Beer 1951)

Starting Mol.: 4-Hydroxy-3-methoxy-ß-methyl-ß-2-dinitrostyrene
Product: 6-Hydroxy-7-methoxy-2-methylindole
Reference: (Beer 1951)

Starting Mol.: 5-Hydroxy-4-methoxy-ß-methyl-ß-2-dinitrostyrene
Product: 5-Hydroxy-6-methoxy-2-methylindole
Reference: (Beer 1951)



4-Methoxy-1-(Phenyl-ß-Nitro-Styrene)



4-Methoxy-6-Nitro-1-(Phenyl-ß-Nitro-Styrene)

Preparation of 4-Methoxy-6-Nitro-1-(Phenyl-ß-Nitro-Styrene) From 4-Methoxy-1-(Phenyl-ß-Nitro-Styrene)

20 Grams (0.12 moles) of 4-methoxy-1-(phenyl-ß-nitro-styrene) is stirred into a solution of 125 mL acetic acid mixed with 75 mL of fuming nitric acid. The solution is kept at 0 degrees for 4 hours and diluted with cold water to precipitate the 4-methoxy-6-nitro-1-(phenyl-ß-nitro-styrene). 4-Methoxy-6-nitro-1-(phenyl-ß-nitro-styrene) can be recrystallized from anhydrous alcohol.

Starting Molecule:ß-Nitro-3:4-methylenedoxy-ß-methylstyrene
Product: 6:ß-Dinitro-3:4-methylenedioxy-ß-methylstyrene
Reference: (Burton 1949)

Alternative Reactions

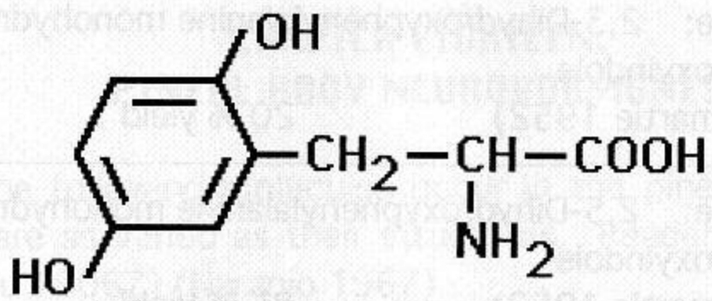
Starting Molecule: 2-Nitro-4,5-dihydroxybenzaldehyde
Reagents: Nitromethane, acetic anhydride
Product: ß:2-Dinitro-4,5-diacetoxystyrene
Reference: (Beer 1948; 1951)

Starting Molecule: 2-Nitro-6-hydroxybenzaldehyde
Reagents: Nitromethane, acetic anhydride
Product: ß:2-Dinitro-6-acetoxystyrene
Reference: (Beer 1948)

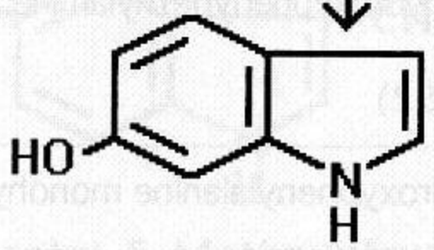
Starting Molecule: 2-Nitro-protocatechuic aldehyde
Reagents: Nitroethane, acetic anhydride
Product: ß:2-Dinitro-4,5-diacetoxy-ß-methylstyrene
Reference: (Partington 1948)

Starting Molecule: 2-Nitro-3,4,5-trimethoxybenzaldhyde
Reagents: Nitromethane
Product: 3,4,5-trimethoxy-2,ß-dinitrostyrene
Reference: (Benington 1960)

Starting Molecule: 2-Nitro-vanillin
Reagents: Nitromethane, acetic anhydride
Product: ß:2-Dinitro-4-acetoxy-5-methoxy-styrene
Reference: (Partington 1948)



2,5-Dihydroxyphenylalanine



5-Hydroxyindole

Preparation of 5-Hydroxyindole From 2,5-Dihydroxyphenylalanine

Solution A:

0.07 Moles of 2,5-dihydroxy-phenylalanine monohydrate and 4.7 grams of sodium bicarbonate is mixed in 350 mL of water.

Solution B:

30 Grams of potassium ferricyanide and 6.9 grams of sodium bicarbonate are mixed in 470 mL of water.

Solution B is added to Solution A over a period of ten minutes with rapid stirring. The solution darkens, and then becomes pale. The mixture is extracted with 1.4 liters of peroxide-free ether or ethyl acetate. The ether or acetate layer is then dried with sodium sulfate and the solvent is evaporated. Colorless needles of 5-hydroxy-indole crystallize. See (Repke 1982) for methylation of hydroxy indoles.

Starting Molecule: 2,3-Dihydroxyphenylalanine monohydrate
Product: 7-Hydroxyindole
Reference: (Cromartie 1952) 20 % yield

Starting Molecule: 2,5-Dihydroxyphenylalanine monohydrate
Product: 5-Hydroxyindole
Reference: (Cromartie 1952) 85 % yield

Starting Molecule: 2-(2,5-Dihydroxyphenyl)ethylamine
Product: 5-Hydroxyindole
Reference: (Harley-Mason 1952)

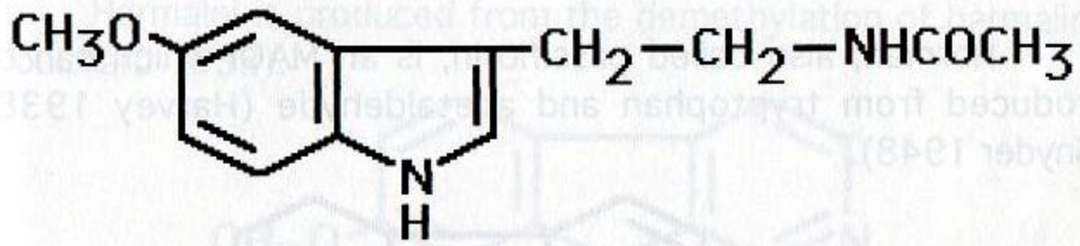
Starting Molecule: 3,4-Dihydroxyphenylalanine monohydrate
Product: 5,6-Dihydroxyindole
Reference: (Bu'Lock 1951)

Starting Molecule: 2,4,5-Trihydroxyphenylethylamine HBr
Product: 5,6-Dihydroxyindole
Reference: (Harley-Mason 1953)

Alternative syntheses of N,N-dialkyl and alpha-alkyl tryptamines, refer to the reduction of ß-indolenideniumethyl nitronate (Heinzelman 1960). ß-Indolenideniumethyl nitronate is prepared from nitroethane and indole-3-aldehyde. Indole-3-aldehyde is prepared from indole and chloroform (Harvey 1938) (Boyd 1935). Grignard Reagents have been used in the production of above described molecules (Bucourt 1960) (Ganellin 1967)

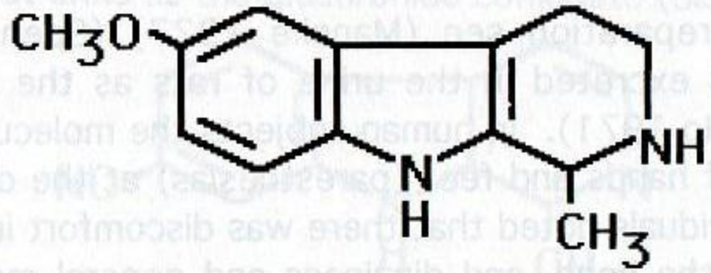
CHAPTER EIGHTEEN:
PINEAL BODY NEUROHORMONES

The following molecules occur in the pineal body. Their effects are as varied as their structures. Readers should check (Deulofeu 19067) (Naranjo 1967).



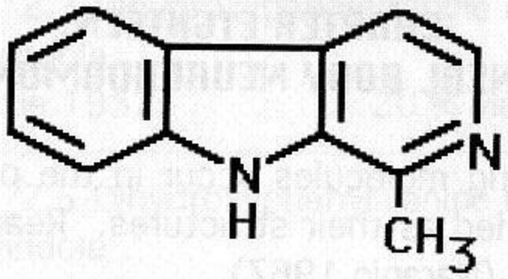
N-Acetyl-5-Methoxytrypamine (Melatonin)

Melatonin occurs in the pineal gland and is the biochemical clock in the brain (Bartsch 1994). Various forms of mental illness may respond to melatonin therapy (Maurizi 1984) (Brown 1995). Melatonin blocks the actions of melanocyte-stimulating and adrenocorticotropic hormones (Axelrod). There are several synthetic methods used to produce melatonin (Szmuszkovicz 1959). Metabolism of melatonin see (Kopin 1961) (Kveder 1961).



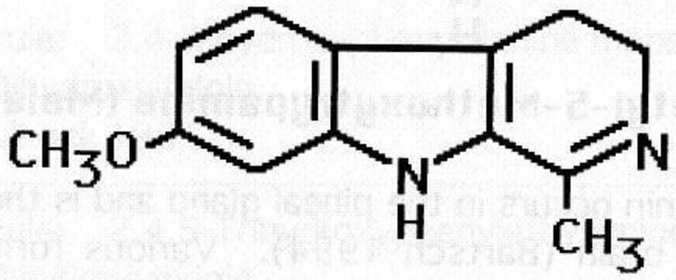
Adrenoglomerulotropin
(6-Methoxytetrahydroharman)

Adrenoglomerulotropin is a hormone of the pineal body. It is an aldosterone-stimulating hormone.



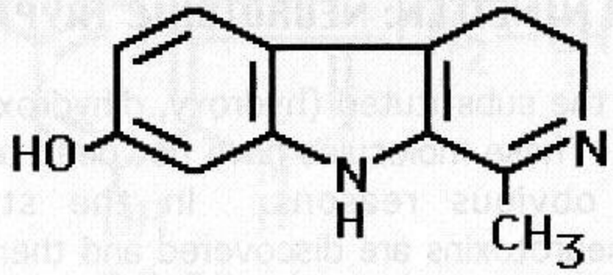
Harman (3-Methyl-4-carboline)

Harman, also called passiflorin, is an MAOI which can be produced from tryptophan and acetaldehyde (Harvey 1938) (Snyder 1948).



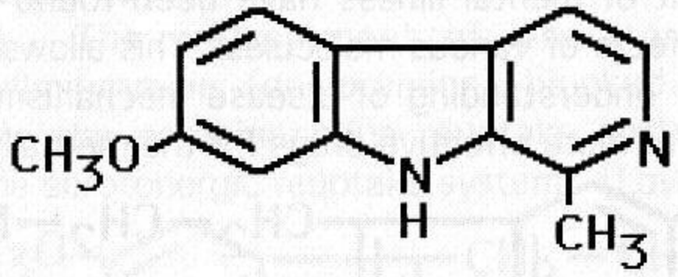
Harmaline

Harmaline is reported to be an inhibitor of MAO A. MAO A mainly deaminates neurotransmitters serotonin, dopamine, tyramine, noradrenalin, and octopamine (Barbeau 1978). The molecule possesses antibacterial activity (Coulthard 1933). Synthetic preparation see (Manske 1927) (Spenser 1959). Harmaline is excreted in the urine of rats as the glucuronide conjugate (Ho 1971). In human subjects the molecule produces numbness of hands and feet (paresthesias) at the onset of the effect. Individuals noted that there was discomfort in the chest, pressure in the head, and dizziness and general malaise which would alternately appear and disappear throughout the session. The dizziness and malaise were associated with certain thoughts or associations (Naranjo 1967). There is a pronouced decrease in neurotic symptoms in many of the subjects who took this molecule.



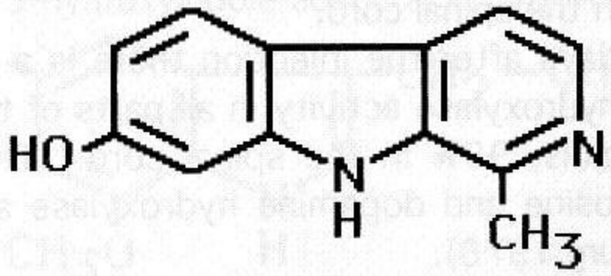
Harmalol

Harmalol is produced from the demethylation of harmaline (Coulthard 1933).



Harmine

Harmine, also called telepathine, has been reported to cause closed eyed visualizations, resembling dream states. This visual effect is not associated with open eyes except by injection in some schizophrenics (Pennes 1957). Oral administation caused only closed eyed visual activity. Telepathine is an MAO inhibitor. Preparation see (Cook 1951) (Harvey 1938). Harmine is excreted in rat urine as the glucuronide conjugate (Slotkin 1970).

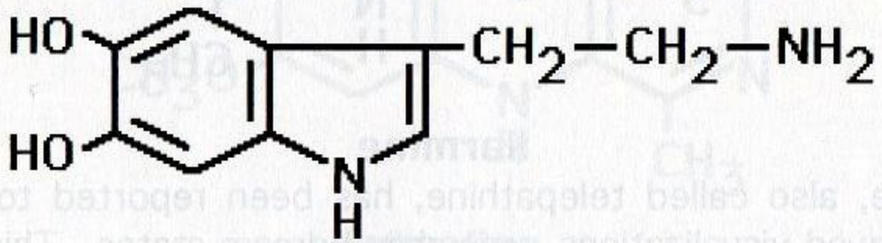


Harmol

Harmol is produced from the demethylation of harmine (Coulthard 1933). ß-Carbolines are also benzodiazepine receptor ligands (Lippke 1983)

CHAPTER NINETEEN: NEUROTOXIC TRYPTAMINES

Many of the substituted (hydroxy, dihydroxy) tryptamines are neurotoxic. These molecules have not been tested in human subjects for obvious reasons. In the study of brain biochemistry, neurotoxins are discovered and then molecules are developed to block the actions of the toxins. Drugs which block these neurotoxic effects might be useful in the treatment of mental illness. In many cases drugs which have been effective in the treatment of mental illness have been found to block the neurotoxic effects of various molecules. This allows scientists to gain a better understanding of disease mechanisms and future development of more effective drugs for the mentally ill.



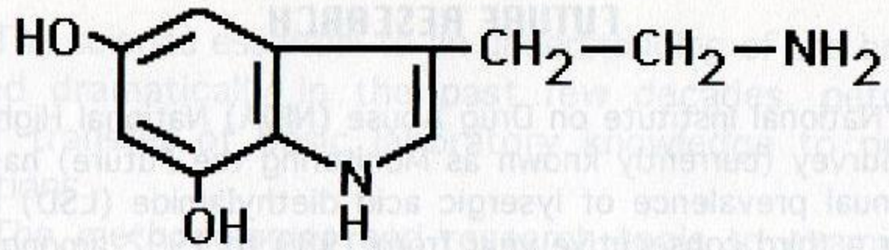
5,6-Dihydroxytryptamine

Injection of 5,6-dihydroxytryptamine (5,6-DHT) in laboratory rats, produces profound reduction of tryptophan hydroxylase in the brain and spinal cord. A week following the injection hydroxylase activity returns to normal in most of the brain, but not in the spinal cord.

Twelve days after the injection there is a significant loss of tryptophan hydroxylase activity in all parts of the brain of the laboratory animals, 95% in the spinal cord. There is also an increase in tyrosine and dopamine hydroxylase activity. (Horn 1978) Lovenburg 1978).

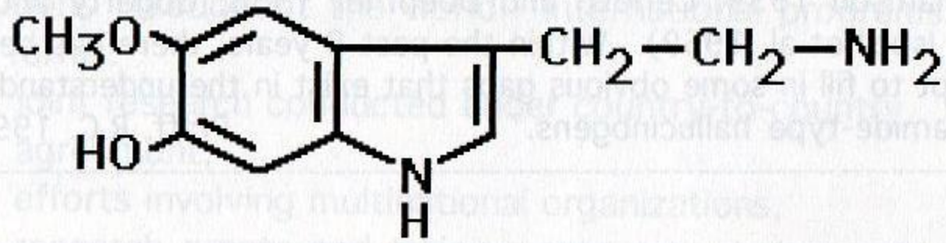
This neurotoxin produced permanent destruction to serotonergic nerve endings and fibers.

Methylation or acetylation of hydroxy groups creates molecules which are not neurotoxic.



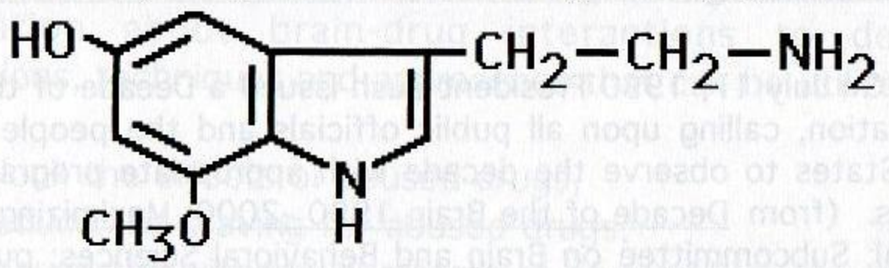
5,7-Dihydroxytryptamine

Injection of 5,7-dihydroxytryptamine in the rat induced a reduction of tryptophan hydroxylase in all regions of the brain. It also caused depletion of norepinephrine, but did not deplete dopamine. The pretreatment of laboratory animals with desmethylimipramine (desipramine) blocked the neurotoxic reaction to the norepinephrine reuptake system, but did not protect the serotonergic reuptake system. (Lovenburg 1978).



6-Hydroxy-5-methoxytryptamine

6-Hydroxy-5-methoxytryptamine produces an increase in exploratory behavior in animals, but not significant from controls. No effect on serotonin & norepinephrine; brief decrease in 5-hydroxyindole acetic acid (5-HIAA). (Maickel 1978)



5-Hydroxy-7-methoxytryptamine

5-Hydroxy-7-methoxytryptamine produced erratic running, vocalization with increased alertness in lab animals. There was no effect on serotonin except for increase in 5-HIAA.

FUTURE RESEARCH

"National Institute on Drug Abuse (NIDA) National High School Senior Survey (currently known as Monitoring the Future) has found that annual prevalence of lysergic acid diethylamide (LSD) use has risen for a third consecutive year from 1989 to 1992 among college students and young adults aged 19 to 28. Moreover, from 1991 to 1992, an increase in LSD use by high school seniors comparable to the increase by college students and a trend of increasing annual prevalence of LSD use by 10th and 8th graders (although at a lower rate for the latter) were also observed..." Lin, G.C. 1994

"The lysergamides have been investigated on several historical occasions, but the late 1950's witnessed most of the recent work (Abrahamson 1959; Cerletti and Doepfner 1958: Gogerty and Dille 1957; Isbell et al. 1959). Within the past 8 years, there has been an attempt to fill in some obvious gaps that exist in the understanding of lysergamide-type hallucinogens." Pfaff, R.C. 1994

"Research in the hallucinogenic drugs (where the desired pharmacological activity can be demonstrated only in humans), the confirmation of activity must occur of necessity in humans. Therefore, it is of potential value for future research in this area to bring together in a single review the known human potencies of the classic hallucinogens and their analogs." Jacob 1994

"On July 17, 1990 President Bush issued a Decade of the Brain Proclamation, calling upon all public officials and the people of the United States to observe the decade with appropriate programs and activities. (from Decade of the Brain 1990 -2000; Maximizing Human Potential; Subcommittee on Brain and Behavioral Sciences; pub. April 1991).

Several developments have converged to make the goals of the Decade of the Brain attainable in the 1990's:

1) The science essential to an understanding of the brain has matured dramatically in the past few decades, permitting greater transfer of basic laboratory knowledge to practical applications.
2) The methodologies and research tools to examine the processes at work in the healthy and unhealthy brain are rapidly maturing.
3) Medical, research and other professional institutions and organizations in the United States and countries around the world are strongly committed to advancing our understanding of the human brain.

To pursue all possible leads about the brain in health and disease, the United States supports and works with scientists in institutions throughout the world. International programs take many forms:

1) joint research conducted under country-to-country agreement,
2) efforts involving multinational organizations,
3) research grants and training programs,
4) collaborative research projects uniting individual U.S. scientists and foreign colleagues, and
5) international meetings to share knowledge.

Investigators will build on the growing foundation of information about brain-drug interactions to develop medications, techniques and approaches that can be utilized to:

1) block the effects of abused drugs,
2) reduce the craving for abused drugs,
3) reduce the withdrawal effects of drug addiction,
4) reverse the toxic effects of abused drugs,
5) develop substitutes for abused drugs with less toxic effects, and
6) prevent the initiation of drug use."

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